

**CARDIOLOGY BOARD REVIEW AND SELF-ASSESSMENT
A COMPANION GUIDE TO**

HURST'S THE HEART

- **1,100+ board review questions**
- **Detailed answer explanations for all questions**
- **Reflects the latest advances in cardiovascular medicine**
- **Comprehensive self-assessment**

CARDIOLOGY BOARD REVIEW AND SELF-ASSESSMENT: A COMPANION GUIDE TO HURST'S THE HEART

For use with the 14th edition of HURST'S THE HEART

EDITED BY

MARK J. EISENBERG, MD, MPH

Professor of Medicine
Cardiology Division
Department of Medicine
Jewish General Hospital
McGill University
Montreal, Quebec, Canada

JONATHAN AFILALO, MD, MSc

Associate Professor of Medicine
Cardiology Division
Department of Medicine
Jewish General Hospital
McGill University
Montreal, Quebec, Canada

JACQUELINE E. JOZA, MD

Assistant Professor of Medicine
Cardiology Division
Department of Medicine
McGill University Health Centre
McGill University
Montreal, Quebec, Canada

RAVI KARRA, MD, MHS

Assistant Professor of Medicine
Cardiology Division
Department of Medicine
Duke University School of Medicine
Durham, North Carolina

PATRICK R. LAWLER, MD, MPH

Assistant Professor of Medicine
Peter Munk Cardiac Centre
Toronto General Hospital
University of Toronto
Toronto, Ontario, Canada



New York Chicago San Francisco Athens London Madrid Mexico City
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CONTRIBUTORS

MARIA L. ALCARAZ, BA

Clinical Research Assistant
Division of Clinical Epidemiology
Department of Medicine
Jewish General Hospital
McGill University
Montreal, Quebec, Canada

EMMANUEL E. EGOM, MD, MSc, PHD

Clinician-Lead for Heart Health Clinic and Hearts in Motion Program
Department of Medicine
St Martha's Regional Hospital
Antigonish, Nova Scotia, Canada

INNA ERMEICHOUK, MSc

Clinical Research Assistant
Division of Clinical Epidemiology
Department of Medicine
Jewish General Hospital
McGill University
Montreal, Quebec, Canada

CAROLINE FRANCK, MSc

Clinical Research Assistant
Division of Clinical Epidemiology
Department of Medicine
Jewish General Hospital/McGill University
Montreal, Quebec, Canada

SARAH B. WINDLE, MPH

Clinical Research Associate
Division of Clinical Epidemiology
Department of Medicine
Jewish General Hospital
McGill University
Montreal, Quebec, Canada

PREFACE

Cardiology Board Review and Self-Assessment is an all-inclusive study guide written to complement the 14th Edition of *Hurst's The Heart*. Edited by Drs. Valentin Fuster, Robert A. Harrington, Jagat Narula, and Zubin J. Eapen, the 14th Edition of *Hurst's The Heart* is an exhaustive and thorough state-of-the-art review of the entire field of cardiovascular medicine.

Cardiology Board Review contains over 1100 questions and answers presented in a multiple-choice format. Each of the 112 chapters of *Hurst's The Heart* is represented in *Cardiology Board Review* with 10 multiple-choice questions. Detailed answers are provided for each question including not only an explanation of why the correct answer is correct but also why incorrect answers are incorrect. Questions and answers correspond to appropriate sections of *Hurst's The Heart* and include tables, figures, and references. The more than 1100 questions presented in *Cardiology Board Review* span the depth and breadth of the fascinating field of cardiovascular medicine.

Cardiology Board Review is designed to be a study guide for individuals preparing to take the Subspecialty Examination in Cardiovascular Disease given by the American Board of Internal Medicine. Thus, *Cardiology Board Review* will be of particular interest to cardiology fellows preparing to take the board examination for the first time and for practicing cardiologists preparing to take the board examination as part of their recertification process. *Cardiology Board Review* will also be of interest to medical students, residents, fellows, practicing physicians, and other health care professionals who wish to advance their knowledge of cardiovascular medicine.

The current generation of health care professionals increasingly obtains their knowledge from nontraditional formats. To that end, *Cardiology Board Review and Self-Assessment* is available in multiple electronic formats in addition to the traditional print format. The book will be available in print, e-book, and online on McGraw-Hill Education's cardiology web site at www.AccessCardiology.com.

It has been my distinct pleasure to work with four coauthors while preparing *Cardiology Board Review*: Drs. Jonathan Afilalo, Jacqueline E. Joza, Ravi Karra, and Patrick R. Lawler. Each of us contributed original questions and answers corresponding to our particular areas of expertise. We would like to thank the members of the editorial and production departments at McGraw-Hill Education with whom we worked, including Karen Edmonson, Robert Pancotti, and Shivani Salhotra. We would also like to acknowledge the contributions and assistance of a number of other individuals, including Maria L. Alcaraz, Emmanuel E. Egom, Inna Ermeichouk, Caroline Franck, and Sarah B. Windle. Finally, on behalf of myself and my coauthors, we would like to express thanks to our families and colleagues for their encouragement and forbearance during the many months it took to prepare this study guide.

Taking care of patients with cardiovascular disease is an honor and a privilege. Many of these patients have life-threatening conditions that require advanced knowledge and highly technical skills. It is our responsibility, as health care professionals, to ensure that our knowledge and skills match the needs of our patients. It is our hope that you will find *Cardiology Board Review and Self-Assessment* to be an essential and valuable tool in your study of the ever expanding and always fascinating field of cardiovascular medicine.

Mark J. Eisenberg, MD, MPH

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SECTION 1

Cardiovascular Disease: Past, Present, and Future

CHAPTER 1

A History of the Cardiac Diseases, and the Development of Cardiovascular Medicine as a Specialty

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

1-1. All of the following were experimental questions asked by William Harvey *except*:

- A. What is the relationship of the motion of the auricle to the ventricle?
- B. Do the arteries distend because of the propulsive force of the heart?
- C. What purpose is served by the orientation of the cardiac and venous valves?
- D. How much blood is present, and how long does its passage take?
- E. All were questions asked by William Harvey

1-2. What were the primary component(s) of the clinical examination until the 17th century?

- A. Palpating the pulse
- B. Palpating the pulse and inspecting the urine
- C. Palpating the pulse and percussion
- D. Palpating the pulse and auscultation
- E. Palpating the pulse, percussion, and auscultation

1-3. Which physician received the Nobel Prize for his work in electrophysiology?

- A. Albert von Kölliker
- B. Heinrich Müller
- C. Augustus Waller
- D. Willem Einthoven
- E. Thomas Lewis

1-4. Who performed the first cardiac catheterization in a human?

- A. Werner Forssmann
- B. Claude Bernard
- C. Dickinson Richards
- D. Etienne Jules Marey
- E. André Cournand

1-5. From which Latin word is the term *angina* appropriated?

- A. Pain
- B. Stress
- C. Strangulation
- D. Anxiety
- E. Discomfort

1-6. Before the defibrillator and coronary care units, the in-hospital mortality associated with acute myocardial infarction was approximately:

- A. 10%
- B. 15%
- C. 20%

- D. 30%
- E. 40%

1-7. Who first described audible heart murmurs?

- A. James Hope
- B. John Mayow
- C. William Cowper
- D. René Laennec
- E. Raymond Vieussens

1-8. Which procedure pioneered by Helen Taussig and Alfred Blalock was a pivotal breakthrough in thinking about congenital heart abnormalities?

- A. Balloon atrial septostomy
- B. Subclavian-pulmonary artery shunt
- C. Closure of atrial septal defect
- D. Closure of ventricular septal defect
- E. Stenting of patent ductus arteriosus

1-9. Who invented the first device for measuring blood pressure?

- A. Etienne Jules Marey
- B. Jean Poiseuille
- C. Scipione Riva-Rocci
- D. Karl von Vierordt
- E. Carl Ludwig

1-10. Which of the following statements about hypertension is *false*?

- A. In 1913, Janeway showed that patients, once diagnosed with hypertensive heart disease and symptoms, lived an average of 4 to 5 years
- B. Until the latter half of the 20th century, the asymptomatic state of most patients with hypertension and a prevalent view that lowering the blood pressure would be deleterious to the kidney and brain lulled most physicians into accepting the condition as being normally associated with aging
- C. Effective oral treatment was available before President Franklin Roosevelt's death in 1945 from severe hypertension
- D. In the 1970s, reports from the Framingham Heart Study showed hypertension to be a major contributing cause to stroke, heart attack, and heart and kidney failure
- E. Richard Bright's 1836 discovery of the relationship of cardiac hypertrophy and dropsy to shrunken kidneys introduced the kidneys as a cause of heart failure long before hypertension was known

ANSWERS

1-1. **The answer is E.** (*Hurst's the Heart, 14th Edition, Chap. 1*) Starting in 1603, Harvey dissected the anatomy and observed the motion of the cardiac chambers and the flow of blood in more than 80 species of animals. His experimental questions "to seek unbiased truth" can be summarized in the following questions: What is the relationship of the motion of the auricle to the ventricle? Which is the systolic and which is the diastolic motion of the heart? Do the arteries distend because of the propulsive force of the heart? What purpose is served by the orientation of the cardiac and venous valves? How does blood travel from the right ventricle to the left side of the heart? Which direction does the blood flow in the veins and the arteries? How much blood is present, and how long does its passage take? After many experiments and without knowledge of the capillary circulation of the lungs, which was not known until 1661, Harvey stated, "It must of necessity be concluded that the blood is driven into a round by a circular motion and that it moves perpetually; and hence does arise the action or function of the heart, which by pulsation it performs." This was published in 1628 as *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*.¹ This revolutionary concept eventually became accepted in Harvey's lifetime and remains the foundation of our understanding of the purpose of the heart.

1-2. **The answer is B.** (*Hurst's the Heart, 14th Edition, Chap. 1*) Until the 17th century, the clinical examination consisted of palpating the pulse and inspecting the urine to reveal disease and predict prognosis. Percussion was first suggested in 1761 by Leopold Auenbrugger, a Viennese physician, who published a book proposing "percussion of the human thorax, whereby, according to the character of the particular sounds thence elicited, an opinion is formed of the internal state of that cavity."² It was reintroduced by Jean-Nicolas Corvisart in early 19th-century France and became an essential addition to the chest examination until it was mostly supplanted by the chest x-ray. While auscultation of the chest was first practiced by Hippocrates (460-370 BC), who applied his ear directly to the chest, it was not until the mid-19th century that the stethoscope (first invented by René Laennec in Paris in 1816) moved auscultation to the forefront of the clinical

examination.^{3,4}

- 1-3. The answer is D.** (*Hurst's the Heart, 14th Edition, Chap. 1*) In 1856, von K  lliker and M  ller demonstrated that the heart also produced electricity. Augustus Waller, with a capillary electrometer device (1887), detected cardiac electricity from the limbs, a crude recording that he called an "electrogram." Willem Einthoven, a physiologist in Utrecht, devised a more sensitive string galvanometer (1902), for which he received the Nobel Prize, and the modern electrocardiogram was born. Initially weighing 600 lb and requiring five people to operate, the three-lead electrocardiograph would eventually become portable, 12 leads, routine, and capable of providing both static and continuous recordings of cardiac rhythm.⁵ With the electrocardiogram, the activation and sequence of stimulation of the human heart could now be measured, and the anatomic basis for the conduction system confirmed. Thomas Lewis in London was the first to realize its great potential, beginning in 1909, and his books on disorders of the heartbeat became essential for aspiring electrocardiographers.^{2,6}
- 1-4. The answer is A.** (*Hurst's the Heart, 14th Edition, Chap. 1*) Claude Bernard in 1844 was the first to insert a catheter into the hearts of animals to measure temperature and pressure.² In the early 1860s, Auguste Chauveau, a veterinary physiologist, and Etienne Jules Marey, inventor of the sphygmograph, collaborated to develop a system of devices called sounds, forerunners of the modern cardiac catheter, which they used to catheterize the right heart and left ventricle of the horse.⁷ Cardiac catheterization in humans was thought an inconceivable risk until Werner Forssmann, a 29-year-old surgical resident in Germany, performed a self-catheterization in 1929.^{8,9} Interested in discovering a method of injecting adrenaline to treat cardiac arrest, Forssmann passed a ureteral catheter into his antecubital vein and confirmed its right atrial position using x-ray. The next year he tried to image his heart using an iodide injection. However, he was reprimanded by superiors and did not experiment further. Catheterization began in earnest in the early 1940s in New York and London. Andr   Cournand and Dickinson Richards at Bellevue, interested in respiratory physiology, developed and demonstrated the safety of complete right heart catheterization, for which they shared the Nobel Prize with Forssmann in 1956.^{7,10}
- 1-5. The answer is C.** (*Hurst's the Heart, 14th Edition, Chap. 1*) On July 21, 1768, William Heberden presented "Some Account of a Disorder of the Breast" to the Royal College of Physicians, London: "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris."^{2,11} Heberden appropriated the term *angina* from the Latin word for strangling. His classic account marks the beginning of our appreciation of coronary artery disease and myocardial ischemia. Edward Jenner and Caleb Parry were the first to suspect a coronary etiology, which Parry published in 1799. Allan Burns, in Scotland, likened the pain of angina pectoris to the discomfort brought about by walking with a tight ligature placed on a limb (1809), a prescient concept that remains relevant today.
- 1-6. The answer is D.** (*Hurst's the Heart, 14th Edition, Chap. 1*) Before the defibrillator and coronary care units, the in-hospital mortality associated with acute myocardial infarction was approximately 30%. With the development of the defibrillator by William Kouwenhoven, Claude Beck and Paul Zoll were able to prove that rescue of cardiac arrest victims was possible. Beck's concept that "the heart is too good to die" instilled optimism into the care of coronary patients and aggressiveness into their providers. Myocardial infarction was no longer a disease to be watched but rather one that might benefit from aggressive therapeutic interventions. Zoll reported closed chest defibrillation in 1956 and cardioversion of ventricular tachycardia in 1960. The monitoring of patients in close proximity to skilled nursing personnel who could perform cardiopulmonary resuscitation was a logical next step suggested by Desmond Julian in 1961.
- 1-7. The answer is D.** (*Hurst's the Heart, 14th Edition, Chap. 1*) Valvular pathology was described in the 17th and 18th centuries; however, Laennec was the first to describe audible heart murmurs, calling them "blowing, sawing, filing, and rasping."³ Originally, he attributed the noises to actual valvular disease, but he later decided that they were caused by spasm or contraction of a cardiac chamber. James Hope in England was the first to classify valvular murmurs in *A Treatise on the Diseases of the Heart and Great Vessels* (1832).¹² He interpreted physical findings in early physiologic terms and provided detailed pathologic correlations.¹³ Constriction of the mitral valve was recorded by John Mayow (1668) and Raymond Vieussens (1715); the latter also recognized that this condition could cause pulmonary congestion.¹⁴ The presystolic murmur of mitral stenosis was described by Bertin (1824), timed as both early diastolic and presystolic by Williams (1835), and placed on firmer grounds by Fauvel (1843) and Gairdner (1861). Aortic stenosis was first described pathologically by Riv  re (1663), and Laennec pointed out that the aortic valve was subject to ossification (1819).¹⁵ Corvisart showed an astute grasp of the natural history of aortic stenosis (1809). Early descriptions of aortic regurgitation were by William Cowper (1706) and Raymond Vieussens (1715),¹⁶ whereas Giovanni Morgagni recognized the hemodynamic consequences of aortic regurgitation (1761). In 1832, Corrigan provided his classic description of the arterial pulse and murmur of aortic regurgitation. Flint added that the presystolic murmur was sometimes heard with severe aortic regurgitation (1862).⁴
- 1-8. The answer is B.** (*Hurst's the Heart, 14th Edition, Chap. 1*) The pivotal breakthrough in thinking about congenital abnormalities came from Helen Taussig and Alfred Blalock at Johns Hopkins Hospital with their "blue baby operation." Taussig had observed that patients with cyanotic heart disease worsened when their ductus arteriosus closed. She suggested creating an artificial ductus to improve oxygenation.¹⁷ Blalock, assisted by Vivian Thomas, successfully created a shunt from the subclavian to the pulmonary artery in November 1944. This innovative operation, in which a blue

baby was dramatically changed to a pink one—the Blalock-Taussig shunt—was highly publicized, and other operations soon followed. These include closure of atrial septal defects (1950s), closure of ventricular septal defects (1954), and tetralogy of Fallot repair (1954). In 1966, Rashkind introduced the balloon septostomy, a novel catheter therapeutic technique that bought time for severely cyanotic infants with transposition of the great arteries.⁷ In the 1980s, catheters were adapted to dilate stenotic aortic and pulmonic valves as well as aortic coarctation. Today, transcatheter closure of patent ductus arteriosus (1971), atrial septal defects (1976), and ventricular septal defects (1987) has become routine. Indomethacin therapy to enable closure of a patent ductus in the premature infant (1976) and prostaglandin infusion to maintain ductal patency (1981) profoundly changed the medical management of fragile newborns. Stents now help keep the ductus open as well as alleviate right ventricular obstruction in tetralogy of Fallot.

- 1-9. The answer is B.** (*Hurst's the Heart, 14th Edition, Chap. 1*) Stephen Hales, an English country parson, reported in his *Statical Essays* (1733) that the arterial blood pressure of the cannulated artery of a recumbent horse rose more than eight feet above the heart—the first true measurement of arterial pressure and the beginning of sphygmometry.^{2,18,19} His pioneering efforts stood alone until 1828 when Jean Poiseuille introduced a mercury manometer device to measure blood pressure.^{20,21} Over the next 60 years, various sphygmomanometric methods were developed—notably by Ludwig (1847), Vierordt (1855), and Marey (1863)—to refine the measurement of the arterial pressure. An inflatable arm cuff coupled to the sphygmograph, a device small enough to allow measurement outside the laboratory, was invented by Riva-Rocci (1896), who also noted the “white-coat effect” on blood pressure.²² Nicolai Korotkoff, a Russian military surgeon, first auscultated brachial arterial sounds (1905), a discovery that marked the advent of modern blood pressure recording. This auscultatory approach eventually ensured its widespread use by the 1920s. In 1939, blood pressure recordings were standardized by committees of the American Heart Association (AHA) and the Cardiac Society of Great Britain and Ireland.
- 1-10. The answer is C.** (*Hurst's the Heart, 14th Edition, Chap. 1*) President Franklin Roosevelt's death in 1945 from severe hypertension and stroke called international attention to the consequences of hypertension and its inadequate treatment—he had been managed with diet, digitalis, and phenobarbital. Effective oral treatment became possible in 1949, first with reserpine and then with hydrochlorothiazide.²³ Lumbar sympathectomy and adrenalectomy (1925), the last resort, was abandoned. Subsequently, β -adrenergic blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blocking agents, and direct renin inhibitors have brought antihypertensive relief to many. Severe salt restriction, as practiced earlier with the Kempner rice diet, has taken a lesser role, whereas the Dietary Approaches to Stop Hypertension (DASH) diet, exercise, and alcohol restriction are encouraged. Since 1973, recommendations published by the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure have been very helpful.

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CHAPTER 2

The Global Burden of Cardiovascular Diseases

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

2-1. How many deaths worldwide are caused each year by cardiovascular disease (CVD)?

- A. 10 million
- B. 15 million
- C. 17 million
- D. 20 million
- E. 23 million

2-2. Which of the following statements about global cardiovascular disease (CVD) is *false*?

- A. There has been a steady decrease in the age-specific death rate for CVD in both sexes over the past 20 years
- B. Women represent 50% of CVD deaths worldwide
- C. The total number of deaths from CVD increased more than 40% between 1990 and 2013
- D. Increases in gross domestic product are well correlated with reductions in cardiovascular disease mortality
- E. A continued increase in the number of CVD deaths is expected as a result of demographic changes worldwide

2-3. What proportion of ischemic heart disease (IHD) patients from low-income world regions are taking *none* of the standard secondary prevention medications?

- A. 20%
- B. 30%
- C. 40%
- D. 60%
- E. 80%

2-4. Which noncommunicable disease (NCD) is the second most common cause of all disability globally?

- A. Stroke
- B. Ischemic heart disease
- C. Chronic obstructive pulmonary disease
- D. Lower back and neck pain
- E. Depression

2-5. Which of the following cardiovascular diseases are more commonly diagnosed in men than in women worldwide?

- A. Abdominal aortic aneurysm
- B. Peripheral arterial disease
- C. Atrial fibrillation
- D. Both A and B
- E. Both A and C

2-6. What is the most common complication of infective endocarditis?

- A. Stroke
- B. Embolization other than stroke
- C. Heart failure
- D. Intracardiac abscess
- E. Intracardiac fistula

2-7. Which of the following statements about Chagas disease is *false*?

- A. Chagas disease is primarily transmitted through the bites of the *Triatoma infestans* insect
- B. No rapid diagnostic tests are available to detect the causative parasite
- C. The acute phase immediately following infection is often asymptomatic, but it produces fever and malaise in up to 5% of people
- D. More than 50% of those infected will not progress to chronic Chagas disease
- E. Approximately 30% of those infected will develop chronic cardiovascular Chagas disease

2-8. What percentage of patients with acute rheumatic fever will develop rheumatic heart disease (RHD)?

- A. 50%
- B. 60%
- C. 70%
- D. 80%
- E. 90%

2-9. Which modifiable cardiovascular risk factor is responsible for the most morbidity and mortality worldwide?

- A. Low fruit intake
- B. High body mass index
- C. High sodium
- D. High blood pressure
- E. Smoking

2-10. In 2013, the WHO and all member states (194 countries) agreed to a Global Non-Communicable Disease (NCD) Action Plan, which aims to reduce the number of premature deaths from NCDs by 25% by 2025 through nine voluntary global targets. Which of the following is *not* one of the nine voluntary targets?

- A. A 20% relative reduction in daily exposure to outdoor and indoor air pollution
- B. A 30% relative reduction in the prevalence of current tobacco use in persons aged 15 years and over
- C. A 25% relative reduction in the prevalence of raised blood pressure or else containing the prevalence of raised blood pressure, according to national circumstances
- D. A halt in the rise of diabetes and obesity
- E. At least 50% of eligible people receiving drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes

ANSWERS

2-1. **The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 2*) In 2013, more than 17 million people died from CVDs, with an estimated US \$863 billion in direct health care costs and productivity losses worldwide.¹ As a result of the large populations in many low- and middle-income countries (LMICs), nearly 70% of CVD deaths occurred in LMICs. CVDs account for 50% of all NCD deaths in the world each year and represent a significant threat to human welfare and sustainable development. CVDs are the leading cause of death in every region of the world, with the exceptions of sub-Saharan Africa—where infectious diseases are still the leading cause of death—and South Korea and Japan, where cancers cause more deaths. The leading cause of CVD-related death was IHD, accounting for more than eight million deaths, followed by ischemic and hemorrhagic strokes, with more than three million deaths each. Rheumatic heart disease, although not the leading cause of death, was a significant contributor to the global burden and a leading cause of highly preventable death, with approximately 275,000 deaths in 2013.

2-2. **The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Despite the steady decrease in death rate for both sexes over the past 20 years, the total number of deaths is increasing as a result of population growth and aging, which disproportionately affects low- and middle-income countries (LMICs). Globally, the total number of CVD deaths increased from 12.3 to 17.3 million, a 41% increase between 1990 and 2013.² Women represent 50% of these deaths. Although most countries have seen an increased national income per capita over this time, the decrease in the number of CVD deaths cannot be entirely explained by economic growth. The decline in age-specific CVD mortality does not correlate well with increases in country income, except weakly in upper-middle income countries. Therefore, it appears unlikely that economic growth alone will improve a country's burden of CVD. Despite an overall decrease in the global age-specific CVD death rate, a continued increase in the number of CVD deaths is expected as a result of demographic changes. The United Nations estimated that the global population in 2015 was 7.3 billion and will increase to a total of 8.5 billion by 2025 and 9.7 billion by 2050. When population growth slows down as a result of a reduction in fertility, the population ages, and the proportion of older persons aged 60 or older increases over time. In 2015, about 10% of the population was aged 60 or older, and the number of adults in this age group is projected to more than double by 2050 and more than triple by 2100, with more than two-thirds of these older adults residing in LMICs.

- 2-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Ischemic heart disease is the leading cause of death worldwide, encompassing myocardial infarction and all other acute coronary syndromes as well as long-term sequelae of coronary heart disease, including angina pectoris and ischemic cardiomyopathy. Since the 1990s, the high-income regions, specifically Australasia, Western Europe, and North America, have seen dramatic declines in the age-standardized IHD mortality.³ However, IHD mortality has increased in other regions, including Central Asia, South Asia, and East Asia. Although IHD burden falls largely on those aged older than 70 years in high-income regions, the age of IHD deaths is much lower in other regions, with a mean age of onset of IHD events before age 50 years in more than 29% of males and 24% of females in North Africa/Middle East and South Asia.^{3,4} As more patients with IHD survive their initial event, the IHD death rate and case fatality will no longer be the sole public health benchmark for success; improved symptom control and overall quality of life and access to adequate treatment will be important secondary outcomes.³ The mainstays of treatment include standard, low-cost medications that are insufficiently used in low- and middle-income countries (LMICs). The Prospective Urban Rural Epidemiological (PURE) study found that only 11% of patients from high-income countries were not taking standard secondary prevention medications, whereas 80% of low-income-region patients were taking none of the recommended medications.^{5,6}
- 2-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Stroke was the second largest contributor to disability globally and in developing countries, whereas it was the third largest contributor to disability in developed countries (after IHD and lower back and neck pain).⁷ Globally, the proportional contribution of stroke-related disability-adjusted life years (DALYs) as a proportion of all diseases increased from 3.5% in 1990 to 4.6% in 2013. The deaths caused by stroke also increased from 9.7% in 1990 to 11.8% in 2013. In order to reduce the rising burden of stroke worldwide, urgent prevention and management strategies are needed. Prevention of risk factors remains key to reversing the stroke pandemic, and universal access to organized stroke services must remain a priority, especially in LMICs.⁸ In 2013, the top five noncommunicable causes of disability globally (from most to least) were: IHD, stroke, lower back and neck pain, chronic obstructive pulmonary disorder, and depression.⁹
- 2-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Abdominal aortic aneurysm (AAA) and atrial fibrillation (AF) are more commonly diagnosed in men than in women worldwide, while peripheral arterial disease (PAD) is equally common among men and women in developed countries, and it is more often diagnosed in women than in men in developing countries. AAA is a focal dilation of the abdominal aorta of at least 1.5 times the normal diameter or an absolute value of 3 cm or greater. Risk factors include male sex, smoking, hypertension, atherosclerosis, and history of AAA in a first-degree relative. In 2010, the age-specific prevalence rate per 100,000 ranged from 7.9 to 2274. Prevalence was higher in developed versus developing nations. The age-specific annual incidence rate per 100,000 ranged between 0.83 and 164.6.¹⁰ AF and atrial flutter are irregular heart rhythms that often cause a rapid heart rate and can increase the risk of stroke, heart failure, and other heart-related complications. In 2010, the estimated age-standardized DALYs resulting from AF was 65 per 100,000 population in males and 46 in females, which was an increase of 18.8% and 19% for males and females since 1990, respectively.¹¹ Higher burden in men compared with women may reflect actual disease rates or poorer access to medical care among women in resource-poor settings. PAD is a circulatory problem in which narrowed arteries reduce blood flow to the limbs and cause symptoms of leg pain with walking (claudication). PAD is defined as an ankle brachial index lower than or equal to 0.90. In developed countries, among adults aged 45–49 years, the prevalence is similar for males and females and is around 5%. The prevalence increases to around 18% for males and females in those aged 85 to 89 years.¹² In developing countries, for the same age groups, the prevalence is around 6% for females and 3% for males and increases to 15% in females and 14% in males.¹²
- 2-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Infective endocarditis (IE) is an infection caused by bacteria, or other infectious pathogens, that enter the bloodstream and cause inflammation in the heart tissues, often on a valve. Because of the lack of direct blood supply, the heart valves are particularly susceptible to bacterial colonization and are neither protected by the typical immune response nor easily reached by antibiotics. IE is a serious illness, with up to 22% in-hospital and 40% five-year mortality rates.¹³ A global collaboration was formed to assess the current characteristics of patients with IE via a large, prospective multicenter registry, called the International Collaboration on Endocarditis (ICE). ICE found that contemporary infective endocarditis is most often an acute disease with a high rate of infection with *Staphylococcus aureus* and involving the mitral (41.1%) and aortic (37.6%) valves. Common complications included stroke (16.9%), embolization other than stroke (22.6%), heart failure (32.3%), and intracardiac abscess (14.4%); these often required surgical intervention (48.2%). In-hospital mortality was high (17.7%).¹⁴ Unfortunately, there were few sites in Asia and Africa included in the registry, which limits the ability to assess geographic differences in patient and microbiologic characteristics in these areas. IE is estimated to have resulted in 65,000 deaths and 1.9 million DALYs in 2013. More complete knowledge and improved surveillance are needed in all world regions.¹⁵
- 2-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Chagas disease is a disease of poverty and is localized to Latin America because it is primarily transmitted through bites from the nocturnal “kissing bug,” *Triatoma infestans*, which is endemic to this region. The infection can be asymptomatic, but it can eventually lead to premature morbidity and mortality, especially in young women of childbearing age. There are rapid diagnostic tests that can detect the causative parasite, *Trypanosoma cruzi*, in serum and can diagnose chronic infections. Pesticides have been developed for vector control programs, but much is still unknown about this disease. In any case, prevention and elimination of the vector remain the keys to Chagas control. The disease has three phases: acute, indeterminate, and chronic. The acute phase immediately follows infection and is often asymptomatic, but it produces fever and malaise in up to 5% of people. The

indeterminate phase is asymptomatic, with more than 50% of those infected remaining in this phase for life without any long-term sequelae. After a decade or more, approximately 30% of people will experience chronic cardiovascular Chagas disease, with symptoms including heart failure, arrhythmias, and thromboembolism.¹⁶ Deaths are rare in the acute phase, and most deaths attributable to Chagas disease result from downstream cardiovascular sequelae. In addition, approximately 15%–20% of people will experience chronic gastrointestinal disease sequelae, including megaesophagus and megacolon. Between 5 and 18 million people are currently infected, and the infection is estimated to cause more than 10,000 deaths annually.¹⁷

- 2-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Rheumatic heart disease is an endemic disease that is common in settings of poverty. It is caused by group A streptococcus infection and leads to mitral stenosis and premature mortality, particularly in young, predominantly female, poorer individuals living in Oceania, South Asia, Central Asia, Africa, and the Middle East. Approximately 60% of all acute rheumatic fever cases will develop RHD, based on data from Aboriginal Australian populations, and 1.5% of patients with RHD will die each year.¹⁸ Globally in 2010, RHD affected more than 34 million people, causing more than 345,000 deaths, almost all in LMICs.¹⁹ The disease can progress to cause moderate to severe multivalvular disease, leading to congestive heart failure, pulmonary hypertension, or AF. RHD also contributes (3%–7.5%) to an estimated 144,000–360,000 incident strokes each year.
- 2-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 2*) Elevated blood pressure is estimated to be the single largest contributor to the global burden of disease and global mortality. There are gaps in the awareness, treatment, and control of hypertension globally. High blood pressure in populations appears to occur in tandem with economic development, but notably in the highest income countries, individuals with lower socioeconomic status are the group most likely to be untreated.^{20,21} In Africa, hypertension is thought to be the leading cause of heart failure, whereas at global levels, hypertension is linked to the development of atherosclerotic vascular disease. In high-income countries, it is estimated to be responsible for 25% of deaths from stroke, 20% of deaths from IHD, and more than 17% of all global deaths.²² The number of people with uncontrolled hypertension was 978 million in 2008, a substantial increase from 605 million in 1980, largely because of population growth and aging.²³ Other modifiable cardiovascular risk factors are: high body mass index, low fruit intake, smoking, high sodium, and high total cholesterol.²⁴
- 2-10. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 2*) While a reduction in exposure to outdoor and indoor air pollution is not one of the nine targets, such pollution ranks as the largest single environmental health risk factor, with more than 2.9 million deaths attributed to outdoor air pollution and a similar number attributed to indoor air pollution.²⁵ Air pollution has been shown to increase preclinical cardiovascular risk factors such as atherosclerosis, endothelial dysfunction, and hypertension. The estimated excess risk of cardiovascular mortality rises 11% per 10 $\mu\text{g}/\text{m}^3$ rise in levels of particulate matter, with no threshold level below which long-term exposure to urban air pollution has no ill effect on cardiovascular health.²⁶ Answers B through E: Modeling studies have shown that significant reductions in premature CVD are possible by 2025 if multiple risk factor targets are achieved. Globally, the risk factor change that would lead to the largest reduction in premature mortality would be the decreased prevalence of hypertension, followed by tobacco smoking prevalence for men and obesity for women.

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CHAPTER 3

Assessing and Improving the Quality of Care in Cardiovascular Medicine

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 3-1.** Which of the following statements concerning health care expenditures in the United States is *false*?
- A. Health care expenditures accounted for nearly 17.5% of the gross domestic product in 2014
 - B. The United States invested an estimated \$3.0 trillion in health care in 2014
 - C. Expenditures related to cardiovascular disease were estimated to be \$656 billion in 2015
 - D. The United States health system ranked lowest among 11 similar countries with respect to access, equity, quality, efficiency, and healthy lives, despite spending the most on health care
 - E. Increasing the use of expensive medical care is associated with better quality of care and patient outcomes
- 3-2.** Which of the following factors influences the variability and appropriateness of health care delivery?
- A. Patients' clinical status
 - B. Sociodemographic factors
 - C. Providers and facilities
 - D. Geographic location
 - E. All of the above
- 3-3.** How many years, on average, does it take for guidelines to be incorporated into clinical practice?
- A. 4 years
 - B. 10 years
 - C. 13 years
 - D. 17 years
 - E. 21 years
- 3-4.** Which of the following is *not* generally considered a part of defining quality of care?
- A. Cost of care
 - B. Evidence-based care
 - C. Improving outcomes
 - D. Patient satisfaction
 - E. All of the above are important for defining quality of care
- 3-5.** Which constitute the primary domains of the Donabedian framework for quality assurance?
- A. Structure, process, and outcome
 - B. Process, outcome, and evaluation
 - C. Research, guidelines, and implementation
 - D. Research, structure, and outcome
 - E. Research, outcome, and cost
- 3-6.** Which of the following is *not* a principal thematic dimension in the Institute of Medicine (IOM)'s landmark report on quality improvement initiatives, *Crossing the Quality Chasm: A New Health System for the 21st Century*?
- A. Safety
 - B. Cost

- C. Timeliness
- D. Efficiency
- E. Equity

3-7. What is the specific function of clinical data standards?

- A. To measure and improve access to evidence-based care
- B. To enable the reproducible collection of data across hospitals and settings
- C. To measure physician performance
- D. To measure the quality of clinical trial data
- E. To enable the assessment of standards of care

3-8. The ACC/AHA guidelines indicate that percutaneous aortic balloon dilation may be considered a bridge to surgical aortic valve replacement or transcatheter aortic valve replacement for symptomatic patients with severe aortic stenosis (Class IIb, level C).²³ A Class IIb level C recommendation could indicate that the intervention is:

- A. Probably indicated, based on data from multiple randomized trials
- B. Probably indicated, based on expert opinion
- C. Probably indicated, based on case studies
- D. Possibly indicated, based on expert opinion
- E. Possibly indicated, based on a single randomized trial

3-9. Which of the following tools for improving the quality of cardiovascular care involves quantifying a range of health care processes and outcomes, identifying multiple points in the continuum of care for which clinical inertia (the failure to implement or titrate recommended therapies) can occur, and then selecting those with the strongest evidence and highest correlation with clinically meaningful outcomes?

- A. Clinical practice guidelines
- B. Clinical data standards
- C. Performance measures
- D. Appropriate use criteria
- E. Procedural registries

3-10. Some of the most exciting opportunities to improve care come from the combination of registries and national coalitions to target significant gaps in care. A dramatic example of this is the Door-to-Balloon (D2B) initiative. Which of the following was *not* a performance recommendation in the D2B initiative?

- A. Prompt data feedback to the emergency department and cath lab staff
- B. Expectations of having the cath lab team assembled within 30 minutes
- C. Targeted times to first ECG acquisition for chest pain patients within 15 minutes
- D. Emergency medicine physician activates cath lab
- E. Single-call activation of the cath lab

ANSWERS

3-1. The answer is E. (*Hurst's the Heart, 14th Edition, Chap. 3*) In the United States, health care expenditures accounted for nearly 17.5% of the gross domestic product in 2014 (an estimated \$3 trillion) and are expected to reach 19.6% by 2024.¹ Cardiovascular disease (CVD) remains the leading cause of death and disability,² with an estimated annual total cost of \$656 billion in 2015.³ In a recent report, the US health system ranked lowest among 11 countries with respect to access, equity, quality, efficiency, and healthy lives,⁴ despite spending the most on health care.⁵ It is often thought that high-quality health care is dependent on the continued discovery and delivery of novel diagnostic and therapeutic interventions. However, studies suggest that greater use of expensive medical care is actually associated with lower quality and worse outcomes.^{6,7} Woolf and Johnson⁸ have extended this concept to mathematically quantify the trade-off between the development of new interventions and the more consistent delivery of known therapies. They argue that despite tremendous scientific and technologic advancements, the failure to consistently deliver proven therapies dilutes and reduces the overall quality of a health care system. Thus, money spent on improving this actual delivery of care may be equally or even more critical than money spent on improving technology to result in improved quality of both routine and specialized health care.

3-2. The answer is E. (*Hurst's the Heart, 14th Edition, Chap. 3*) A critical goal of efforts to disseminate high-quality care is to ensure rational and efficient use of effective treatment to those who derive the most benefit.⁹ Yet surveys evaluating processes of care have shown that, on an average, only one in two US adults receives recommended care when receiving health care services.¹⁰ Several studies have suggested that there are marked variations in the use of evidence-based

treatments of cardiovascular disease (CVD) based on gender, age, race, education, income, and insurance status.^{10,11,12,13} A study examining differences in the treatment of myocardial infarction showed that although blacks lived closer than whites to hospitals with revascularization capability that were considered high-quality, they were less likely than whites to be admitted to revascularization-capable and high-quality hospitals.¹⁴ Further emphasizing the need to monitor the quality of care has been the observation of marked variations in the processes of care by geographic region. Pioneering work from the Dartmouth Atlas series, a comprehensive evaluation of health care services provided to Medicare beneficiaries, has documented broad variation in the use of both diagnostic and treatment modalities in CVD as a function of the site of care.¹⁵ Beyond concerns about overall disparities in care, there is emerging evidence that among the patients eligible for treatments, those with the least potential to benefit are preferentially treated, whereas those with the most to gain are systematically undertreated. This finding is referred to as the *risk-treatment paradox*. Many investigators have shown that high-risk patients—who would be expected to benefit more than lower-risk patients—are treated less aggressively, whereas lower-risk patients are treated more aggressively.^{16,17}

- 3-3. The answer is D.** (*Hurst's the Heart, 14th Edition, Chap. 3*) It is estimated that, on average, it takes about 17 years for guidelines to be incorporated into clinical practice,⁹ even with an intervention as simple as aspirin use at the time of myocardial infarction (> 20 years for full adoption). There can be several levels of barriers to the effective implementation of clinical evidence and guidelines in routine practice. These exist at policy, societal, system/organizational, provider, and patient levels. These can be addressed through the use of frameworks for quality metrics and tools to improve quality of care in cardiovascular disease.
- 3-4. The answer is E.** (*Hurst's the Heart, 14th Edition, Chap. 3*) Lohr and Schroeder broadly define quality of care as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”¹⁸ The US Agency for Healthcare Research and Quality has proposed a similar definition: “Quality healthcare means doing the right thing at the right time in the right way for the right person and having the best results possible.”¹⁹ The Institute for Healthcare Improvement recommends that to improve the United States' health care system requires simultaneous pursuit of three aims, called the “Triple Aim”—improving the patient experience of care (including satisfaction), improving outcomes (of individuals and populations), and reducing the per capita cost of health care.²⁰ Achieving the best quality of care as marked by highest quality patient outcome and experience with the lowest possible cost is what a health care system usually strives to achieve. Although the concept of quality health care is intuitive and relatively easy to understand, to actually measure, monitor, and improve quality requires the use of a clear conceptual framework that encompasses important, relevant aspects of health care.
- 3-5. The answer is A.** (*Hurst's the Heart, 14th Edition, Chap. 3*) One of the earliest approaches to conceptualizing the components of quality assurance was proposed by Donabedian.²¹ This framework considers quality to comprise three main domains: structure, process, and outcome. Structure refers to the attributes of settings where care is delivered and includes aspects that exist independently of the patient. Examples of structural attributes include provider training and experience, the availability of specialized treatments, nurse-to-patient ratios, and treatment and discharge plans. Process refers to whether or not good medical practices are followed, and it incorporates concepts such as the medications given and the timing of their administration, the use of diagnostic and therapeutic procedures, and patient counseling. Outcome refers to tangible measures that capture the consequences of care and range from manifestations of disease progression (eg, mortality and hospitalizations) to patient-centered outcomes of health status and treatment satisfaction. As noted by Donabedian, these three components of quality are interdependent and are built on a framework that focuses mainly on linking the delivery of care to outcomes.
- 3-6. The answer is B.** (*Hurst's the Heart, 14th Edition, Chap. 3*) The current driving force and roadmap for quality improvement initiatives in American health care is the Institute of Medicine (IOM)'s landmark report, *Crossing the Quality Chasm: A New Health System for the 21st Century*.⁹ The IOM recognized the following principal thematic dimensions needed to guide QI in health care:
- Safety—avoiding injuries to patients from the care that is intended to help them
 - Effectiveness—providing services based on scientific knowledge to those who could benefit while refraining from providing services to those not likely to benefit
 - Patient-centeredness—providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions
 - Timeliness—reducing waits and sometimes harmful delays in care
 - Efficiency—avoiding waste, including waste of equipment, supplies, ideas, and energy
 - Equity—providing care that does not vary in quality because of personal characteristics such as sex, ethnicity, geographic location, and socioeconomic status
- Cost is not one of the principal themes of the IOM report, but it is considered among the outcomes in the Donabedian framework for quality assurance.
- 3-7. The answer is B.** (*Hurst's the Heart, 14th Edition, Chap. 3*) To measure and improve care, one first needs to know both how and what to measure. It is critical to have standardized data definitions that enable the reproducible collection of data across different hospitals and settings. To create the foundation for clear, explicit data capture, the ACC/AHA Clinical Data Standards were developed to serve as a foundation for implementing and evaluating the other ACC/AHA quality

tools.²² These data standards are a set of standardized definitions of particular conditions and treatments that can and should be applied in both QA/QI activities and, importantly, clinical trials. Inclusion in clinical trials is especially important to support both comparability across studies and their incorporation into guidelines, performance measures, and clinical care. In particular, standardized definitions support the consistent definition of symptoms, comorbidities, and outcomes in many areas of CVD (eg, acute coronary syndromes, congestive heart failure, PCI).²² The more these data standards are used in clinical trials, observational registries, and QA/QI efforts, the greater the ability will be to translate the emerging knowledge from clinical research to clinical care.

- 3-8. The answer is D.** (*Hurst's the Heart, 14th Edition, Chap. 3*) To distill the rapidly expanding body of cardiovascular literature, professional agencies, such as the AHA and ACC, have commissioned expert committees to synthesize the available evidence into clinical practice guidelines.²⁴⁻²⁵ The creation of guidelines requires writing committees to systematically review the medical literature and to assess the strength of evidence for particular treatment strategies. This necessitates ranking the types of research from which knowledge is generated. Randomized controlled trials are given the highest weight. When these are not available, other study designs, including preintervention and postintervention studies, observational registries, and clinical experience are used. To transparently communicate the strength of a recommendation and the evidence on which it is generated, a class recommendation (Class I = strongly indicated, Class IIa = probably indicated, Class IIb = possibly indicated, or Class III = not indicated) and strength of the evidence (level A evidence [data derived from multiple randomized trials] through level C [data derived from expert opinion, case studies, or standard of care]) are provided.²⁵ An intervention that is probably indicated, based on data from multiple randomized trials (option A) is a Class IIa level A recommendation. An intervention that is probably indicated, based on expert opinion (option B) or probably indicated, based on case studies (option C) are both Class IIa level C recommendations. An intervention that is possibly indicated, based on a single randomized trial (option E), is a Class IIb level B recommendation.
- 3-9. The answer is C.** (*Hurst's the Heart, 14th Edition, Chap. 3*) At times, the evidence supporting (or for avoiding) a particular diagnostic or therapeutic action is so strong that failure to perform such actions jeopardizes patients' outcomes. Performance measures represent that subset of the clinical practice guidelines (option A) for which the strongest evidence exists and for which their routine use (or avoidance) is felt to be an important advance to elevating quality.^{26,27,28} Performance measures are often constructed as a set of measures that quantify a range of health care processes and outcomes; they are designed to identify multiple points in the continuum of care for which clinical inertia—the failure to implement or titrate recommended therapies—can occur.^{28,29} Once the relevant domains are identified, then those guideline recommendations with the strongest evidence and highest correlation with clinically meaningful outcomes are selected for performance measure creation. Clinical data standards (option B) are a set of standardized definitions of particular conditions and treatments that can be applied in both quality assurance/improvement activities and clinical trials. Appropriate use criteria (option D) help identify what specific tests and procedures to perform and when and how often, based on estimates of the relative benefits and harms of a procedure or a test for a specific indication. Procedural registries (option E) support the prospective collection of data for assessing performance and guideline compliance within hospitals.
- 3-10. The answer is C.** (*Hurst's the Heart, 14th Edition, Chap. 3*) First ECG acquisition for chest pain patients was recommended within 10 minutes. Launched in 2006, the Door-to-Balloon (D2B) initiative sought to increase the proportion of ST-segment elevation myocardial infarction patients receiving primary PCI within 90 minutes of hospital presentation from approximately 50% to more than 75%.³⁰ This program supplemented data collected through the NCDR CathPCI registry with explicit recommendations about how to improve performance,³¹ including (1) activation of the catheterization laboratory (cath lab) by emergency department physicians, (2) single-call activation of the cath lab, (3) expectations of having the cath lab team assembled within 30 minutes, (4) prompt data feedback to the emergency department and cath lab staff, and (5) activation of the cath lab based on prehospital ECGs and targeted times to first ECG acquisition for chest pain patients within 10 minutes. Between January 2005 and September 2010, this effort led to a decline in median D2B time, from 96 minutes in December 2005 to 64 minutes in September 2010.³² There were corresponding increases in the proportion of patients undergoing primary PCI within 90 minutes (from 44.2% to 91.4%), and within 75 minutes (from 27.3% to 70.4%). The declines in median times were greatest among groups that had the highest median times during the first period.³²

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SECTION 2

Foundations of Cardiovascular Medicine

Functional Anatomy of the Heart

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

4-1. Which of the following statements is *false*?

- A. The main pulmonary artery, portions of both venae cavae, distal pulmonary veins, and nearly the entire ascending aorta are intrapericardial
- B. The right and left pulmonary arteries are extrapericardial structures
- C. The transverse sinus forms a tunnel-like passageway that separates the great arteries anteriorly from the great veins posteriorly
- D. The oblique sinus lies posterior to the right atrium
- E. The serous pericardium forms the inner lining of the fibrous pericardium; over the heart, it is referred to as the epicardium

4-2. A 35-year-old woman presents to your clinic for evaluation of a murmur. She describes intermittent regular palpitations that have been associated with lightheadedness. Auscultation reveals a midsystolic click and a crescendo systolic murmur. The S1-click distance increases with squatting and decreases with standing. Regarding this valve or valve defect, which statement is *true*?

- A. The valve leaflets are characteristically thin
- B. Annular dilatation is not typically present
- C. Prolapse of the anterior leaflet occurs more frequently
- D. The anterolateral papillary muscle is commonly single and usually has a dual blood supply from the left coronary circulation
- E. The posteromedial papillary muscle usually has a single head and is most commonly supplied by the left anterior descending artery

4-3. Regarding [Figure 4-1](#), select the statement that is *false*:

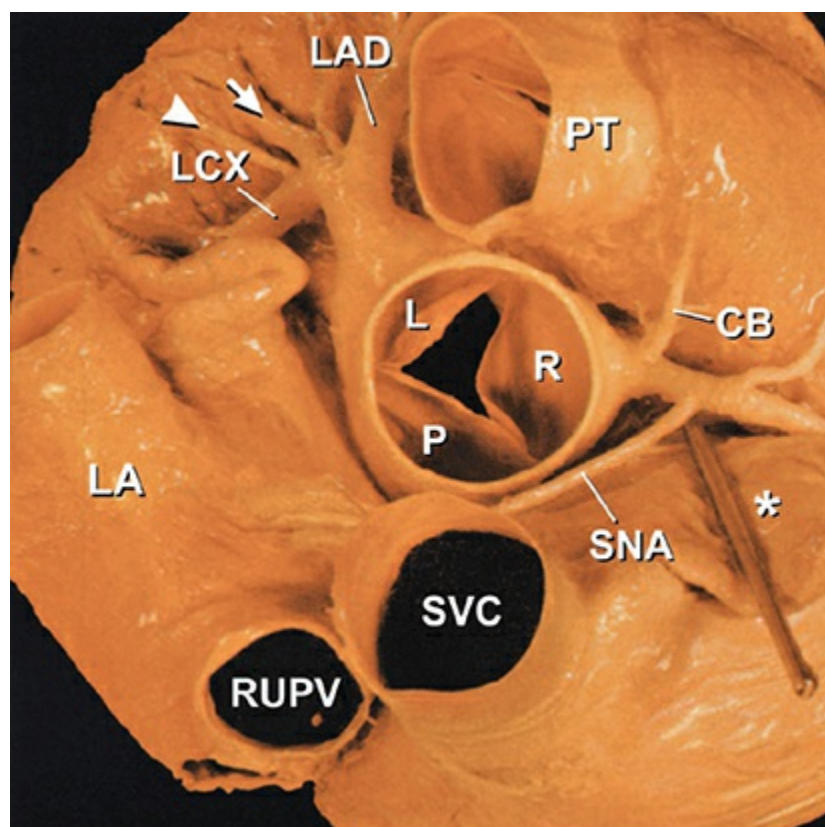


FIGURE 4-1 Superior view of the heart. (Reproduced with permission from McAlpine W. *Heart and Coronary Arteries: An Anatomic Atlas for Radiologic Diagnosis and Surgical Treatment*. New York: Springer-Verlag; 1975.)

- A. The central structures labelled L, P, and R are supplied by the conus artery
- B. The * depicts the right atrial appendage
- C. The arrowhead points to a circumflex marginal branch
- D. An ablation catheter positioned at P will reveal atrial electrogram signals
- E. The oblique sinus is not visualized in this figure

4-4. All of the following are used to differentiate the right ventricle from the left ventricle *except*:

- A. The presence of a moderator band
- B. Free wall typically < 0.4 mm thick
- C. A prominent arch-shaped muscular ridge known as the crista supraventricularis separates the tricuspid and pulmonary valves
- D. The apex is thin and lacks trabeculation
- E. The tricuspid valve always follows the morphological right ventricle

4-5. Which of the following statements regarding structures within the right atrium is *false*?

- A. The cavotricuspid isthmus is targeted during typical right atrial flutter ablation
- B. The cavotricuspid isthmus is a well-defined region of atrial tissue that is bordered by the eustachian ridge and valve posteriorly, and the tricuspid valve annulus anteriorly
- C. The right atrial free wall is a very thin structure between pectinate muscles and can perforate during catheter positioning
- D. Inferior vena caval blood flow is directed by the eustachian valve toward the foramen ovale, and superior vena caval blood is directed toward the tricuspid valve
- E. The right atrial appendage abuts the left aortic sinus of Valsalva

4-6. A patient undergoes a transesophageal echocardiography (TEE) as workup for possible left atrial appendage (LAA) closure. Regarding the LAA, which of the following statements is *false*?

- A. There is no known relationship between stroke and LAA morphology
- B. There are four basic morphologic patterns to the LAA: windsock, cactus, cauliflower, and chicken wing
- C. Age is not a determinant for the dimensions of an LAA
- D. All lobes of the LAA should be visualized during TEE to rule out a thrombus
- E. Both the right and the left atrial appendages are located close to the right ventricular outflow tract

4-7. All of the following are true statements *except*:

- A. The left anterior descending artery courses within the epicardial fat of the anterior interventricular groove
- B. The first septal perforating branch of the left anterior descending artery supplies the AV (His) bundle and proximal left bundle branch
- C. Dominance is left in 70% of human hearts, right in 10%, and shared in 20%
- D. A patient who presents acutely with an anterior ST elevation myocardial infarction secondary to a left anterior descending artery occlusion is at risk for a mechanical complication
- E. The right coronary artery typically arises nearly perpendicularly from the aorta

4-8. In a typical right-dominant system, which of the following left ventricular segments would most likely *not* be affected in a patient with left anterior descending artery occlusion?

- A. Mid anterior wall
- B. Mid inferolateral wall
- C. Basal anterior septum
- D. Basal anterior wall
- E. Mid anterolateral wall

4-9. Regarding the great vessels, which of the following statements is *true*?

- A. Most coarctations occur just proximal to the left subclavian artery
- B. When the eustachian or the adjacent thebesian valve of the coronary sinus is large and fenestrated, it is referred to as the ligamentum arteriosum
- C. The ligamentum arteriosum represents the vestigial remnant of the fetal ductal artery, which, when patent, connects the proximal right pulmonary artery to the undersurface of the aortic arch
- D. The ostium of the superior vena cava (SVC) is guarded by a crescent-shaped, often fenestrated flap of tissue called the eustachian valve
- E. The ligament of Marshall is the vestigial remnant of the vein of Marshall, which forms the terminal connection between a persistent left SVC and the coronary sinus

4-10. Which of the following statements is *false* concerning the triangle of Koch?

- A. It is bordered by the coronary sinus ostium, the septal tricuspid annulus, and the tendon of Todaro
- B. The AV node is a subendocardial structure that is located within the upper portion of the triangle of Koch

- C. The His bundle is located within the triangle of Koch. The apex of the triangle corresponds to the central fibrous body of the heart where the His bundle penetrates
- D. The atrial end of the fast pathway in AV nodal reentrant tachycardia inserts near the ostium of the coronary sinus, while the slow pathway lies closer to the apex of the triangle near the AV node
- E. AV node displacement occurs in Ebstein malformation and persistent left SVC

ANSWERS

- 4-1. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The reflections along the pulmonary veins and venae cavae are continuous and form a posterior midline cul-de-sac known as the oblique sinus. The oblique sinus lies immediately posterior to the left atrium, *not* the right atrium (option D). The main pulmonary artery, portions of both venae cavae, distal pulmonary veins, and nearly the entire ascending aorta are intrapericardial (option A). The right and left pulmonary arteries are extrapericardial structures (option B). The transverse sinus forms a tunnel-like passageway that separates the great arteries anteriorly from the great veins posteriorly (option C). The serous pericardium forms the delicate inner lining of the fibrous pericardium and continues onto the surface of the heart and great vessels at the pericardial reflection.¹ Over the heart, it is referred to as the epicardium, and it contains the epicardial coronary arteries and veins, autonomic nerves, lymphatics, and a variable amount of adipose tissue (option E).
- 4-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The anterolateral papillary muscle is single and usually has a dual blood supply from the left coronary circulation (option D).² Mitral valve prolapse is characterized by *thickened* and redundant leaflets (option A), annular dilatation (with or without calcium) and thickened and elongated chordae tendineae (with or without rupture) (option B). Prolapse of the posterior leaflet occurs more often than that of the anterior leaflet (option C). The posteromedial papillary muscle usually has multiple heads and is most commonly supplied only by the dominant coronary artery (option E).² Small left atrial branches supply the most basal aspects of the mitral leaflets.³
- 4-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The figure shows a superior view of the heart, including the aortic and pulmonic valves, the origins of the left and right coronary arteries, the superior aspect of the left atrium, the SVC, and the right upper pulmonary vein. The aortic cusps (labeled L for left aortic cusp; P for posterior aortic cusp; and R for right aortic cusp) form pocketlike tissue flaps that are avascular (option A). The conus artery is the first branch of the right coronary artery in 50%–60% of persons; it supplies the right ventricular outflow tract and forms an important collateral anastomosis (circle of Vieussens) just below the pulmonary valve with an analogous branch from the left anterior descending coronary artery.¹⁻³ The * symbol (option B) represents the right atrial appendage, which is retracted by the rod to disclose the sinus node artery (SNA). The arrowhead (option C) is pointing to a marginal branch of the left circumflex artery. An ablation catheter positioned at the posterior (or noncoronary) cusp (option D) will reveal atrial electrogram signals due to its close proximity to the interatrial septum. The oblique sinus (option E) is not seen in this figure. It is formed from the reflections along the pulmonary veins and venae cavae that form a posterior midline cul-de-sac that lies posterior to the left atrium.
- 4-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The right ventricular apex is heavily trabeculated.^{1,3} This apical trabecular zone extends inferiorly beyond the attachments of the papillary muscles toward the ventricular apex and about halfway along the anterior wall. This muscular meshwork is the usual site of insertion of transvenous ventricular pacemaker electrodes, and it is the preferred site for positioning the tip of an implantable cardioverter defibrillator lead. The moderator band (option A) forms an intracavitary muscle that connects the septal band with the anterior tricuspid papillary muscle. The right ventricular wall is thin in normal adults, usually less than 0.4 cm (regional variation between 0.2 and 0.7 cm) (option B). A prominent arch-shaped muscular ridge known as the crista supraventricularis separates the tricuspid and pulmonary valves. It is made up of three components (parietal band, infundibular septum, and septal band) that can appear as distinct structures or can merge together (option C).^{1,3} The tricuspid valve always follows the morphological right ventricle, which is an important consideration when evaluating patients with congenital heart disease (option E).
- 4-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The right atrial appendage abuts the right aortic sinus of Valsalva and overlies the proximal right coronary artery (option E). The cavotricuspid isthmus, a frequent target of atrial flutter ablation, is a well-defined region of atrial tissue that is bordered by (1) the eustachian ridge and valve posteriorly and (2) the tricuspid valve annulus anteriorly (options A, B). The right atrial free wall is paper-thin between pectinate muscles and therefore can be perforated easily by stiff catheters (option C).¹⁻³ The atrial lead of a dual-chamber pacemaker is normally positioned within the trabeculations of the right atrial appendage. Inferior vena caval blood flow is directed by the eustachian valve toward the foramen ovale, and superior vena caval blood is directed toward the tricuspid valve (option D).⁴
- 4-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The left atrial appendage is usually multilobed and narrower than its right atrial counterpart, and it exhibits more variability in shape.^{1-3,5} The chicken wing variety of LAA

morphology has the *least* likelihood for embolic events (option A).⁶ There are four basic morphologic patterns: windsock, cactus, cauliflower, and chicken wing (option B).⁶ Age and sex are both determinants for LAA dimension (option C).⁴ There may be multiple lobes in the LAA; all lobes must be visualized in order to rule out thrombus prior to planned cardioversion, electrophysiology or structural procedure, or percutaneous balloon valvuloplasty procedures (option D). Either atrial appendage may serve as a vantage point from which to access and ablate arrhythmias in the adjacent segment of the right ventricular outflow tract (option E).⁷

- 4-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 4*) Dominance is right in 70% of human hearts, left in 10%, and shared in 20%.¹⁻³ In patients with a congenitally bicuspid aortic valve, the incidence of left coronary dominance is 25% to 30%.³ The left anterior descending artery (LAD) courses within the epicardial fat of the anterior interventricular groove (option A). The first septal perforating branch supplies the AV (His) bundle and the proximal left bundle branch (option B).³ In patients with symptomatic hypertrophic obstructive cardiomyopathy, nonsurgical septal reduction by percutaneous transluminal occlusion of septal branches of the LAD is a therapeutic approach aimed at reducing the outflow gradient.⁸ Anterior infarcts have been shown to be independent predictors of ventricular septal defects post myocardial infarction (option D). Whereas the right coronary artery arises almost perpendicularly from the aorta, the left arises at an acute angle (option E).⁴
- 4-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 4*). The midventricular inferolateral wall is typically supplied by the *circumflex artery*, not the left anterior descending artery (LAD). In a typical right-dominant system, the LAD supplies the midventricular and basal segments of the anterior (options A and D), anterolateral walls (option E) and anterior septum (option C) and all apical segments. The left circumflex artery supplies the midventricular and basal inferolateral segments, and the right coronary artery supplies the midventricular and basal inferior wall and inferior septum. In the setting of a large obtuse marginal branch of the circumflex artery, the anterolateral or inferior wall may not be supplied by the LAD. However, because the patterns of coronary distribution are so highly variable, these correlations between coronary blood flow and regional anatomy are not precise. For example, a hyperdominant right coronary artery can supply the apex, and a large, obtuse marginal branch of the circumflex artery can supply the anterolateral or inferior wall.¹⁻³ Ventricular septal defects are more common in the setting of a wrap-around LAD.
- 4-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The vein of Marshall forms the terminal connection between a persistent left SVC and the coronary sinus. Its vestigial remnant in normal adults is the ligament of Marshall; it is a potential source of arrhythmias and a common site for recurrences after pulmonary vein isolation (option E). Most coarctations occur just *distal* to the left subclavian artery (option A). The ostium of the inferior vena cava is guarded by a crescent-shaped, often fenestrated flap of tissue, the eustachian valve,¹⁻³ which is readily seen by echocardiography. Although generally small, the eustachian valve can become so large that it can produce a double-chambered right atrium.² Also, when either the eustachian or the adjacent thebesian valve of the coronary sinus is large and fenestrated, it is referred to as a Chiari network (option B).¹⁻³ The ligamentum arteriosum represents the vestigial remnant of the fetal ductal artery, which, when patent, connects the proximal *left* pulmonary artery to the undersurface of the aortic arch (option C). The ostium of the *inferior* vena cava (not the SVC) is guarded by the eustachian valve. It is an important structure during cavotricuspid isthmus ablation (option D).
- 4-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 4*) The atrial end of the fast pathway in AV nodal reentrant tachycardia inserts closer to the AV node at the apex of the triangle, whereas the slow pathway (target for radiofrequency ablation) inserts near the ostium of the coronary sinus (option D). The triangle of Koch is bordered by the coronary sinus ostium posteroinferiorly, the septal tricuspid annulus anteriorly, and the tendon of Todaro posteriorly (option A). The tendon of Todaro is a fibrous extension of the Eustachian valve (option B). The body of the AV node is found near the apex of the triangle. The His bundle, also located in the triangle of Koch, penetrates through the central fibrous body separating the atria and ventricles (option C). The bundle of His then bifurcates into right and left main bundle branches, which branch further to become Purkinje fibers that spread conduction to the ventricles. Differences in the conduction system primarily reside in the arrangement of the transitional and compact components of the AV node and in the length and route of the His bundle. In both Ebstein's anomaly and persistent left SVC syndrome with a grossly enlarged CS ostium, the size of the triangle of Koch is reduced, resulting in a shorter distance between the compact AV node and the CS ostium (option E).

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CHAPTER 5

Normal Physiology of the Cardiovascular System

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

5-1. Which of the following is *true* about Figure 5-1?

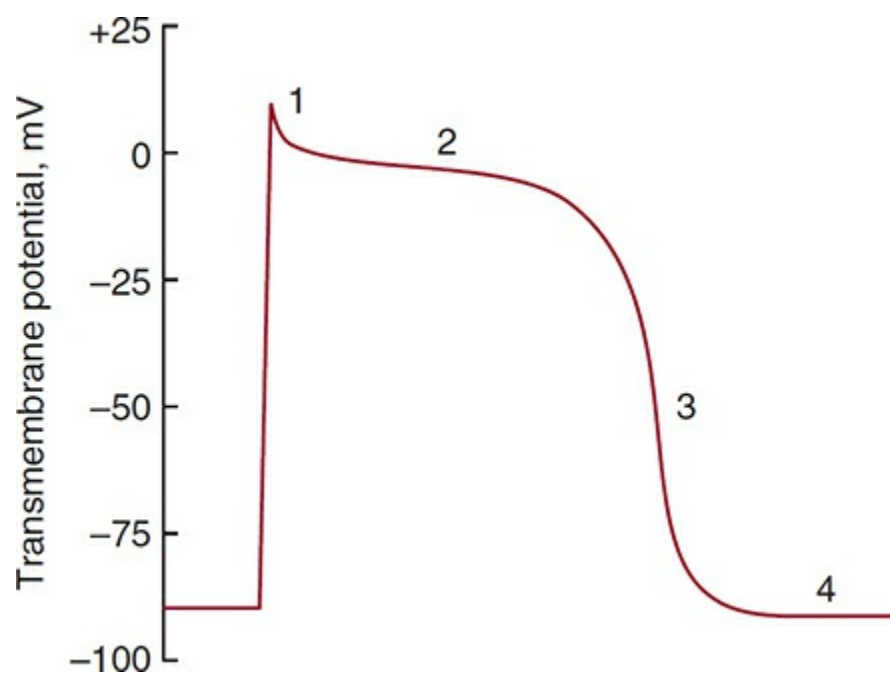


FIGURE 5-1 Phases of the action potential and major associated currents in ventricular myocytes.

- A. Sodium influx during phase 1 depolarization is decreased by membrane depolarization
 - B. Sodium influx is limited after phase 1 by the closure of inactivation gates
 - C. The phase 2 plateau of the action potential is the result of a decrease in intracellular calcium through the L-type calcium channel
 - D. Phase 3 repolarization is the result of potassium influx into the cell through the funny channel (I_F)
 - E. Maintenance of the membrane potential during diastole is an energy-independent process
- 5-2. Please select the *true* statement about Figure 5-2.
- A. Calcium-induced calcium release occurs by calcium influx through ion channel B with release of calcium from the sarcoplasmic reticulum via ion channel C
 - B. The magnitude of the calcium transient is, in part, determined by calcium influx into the cell via channels B and D
 - C. The decline in the calcium transient occurs via channel C and is energy-independent
 - D. Increased cytoplasmic calcium results in contraction, in part, by the binding of calcium to TnI
 - E. None of the above

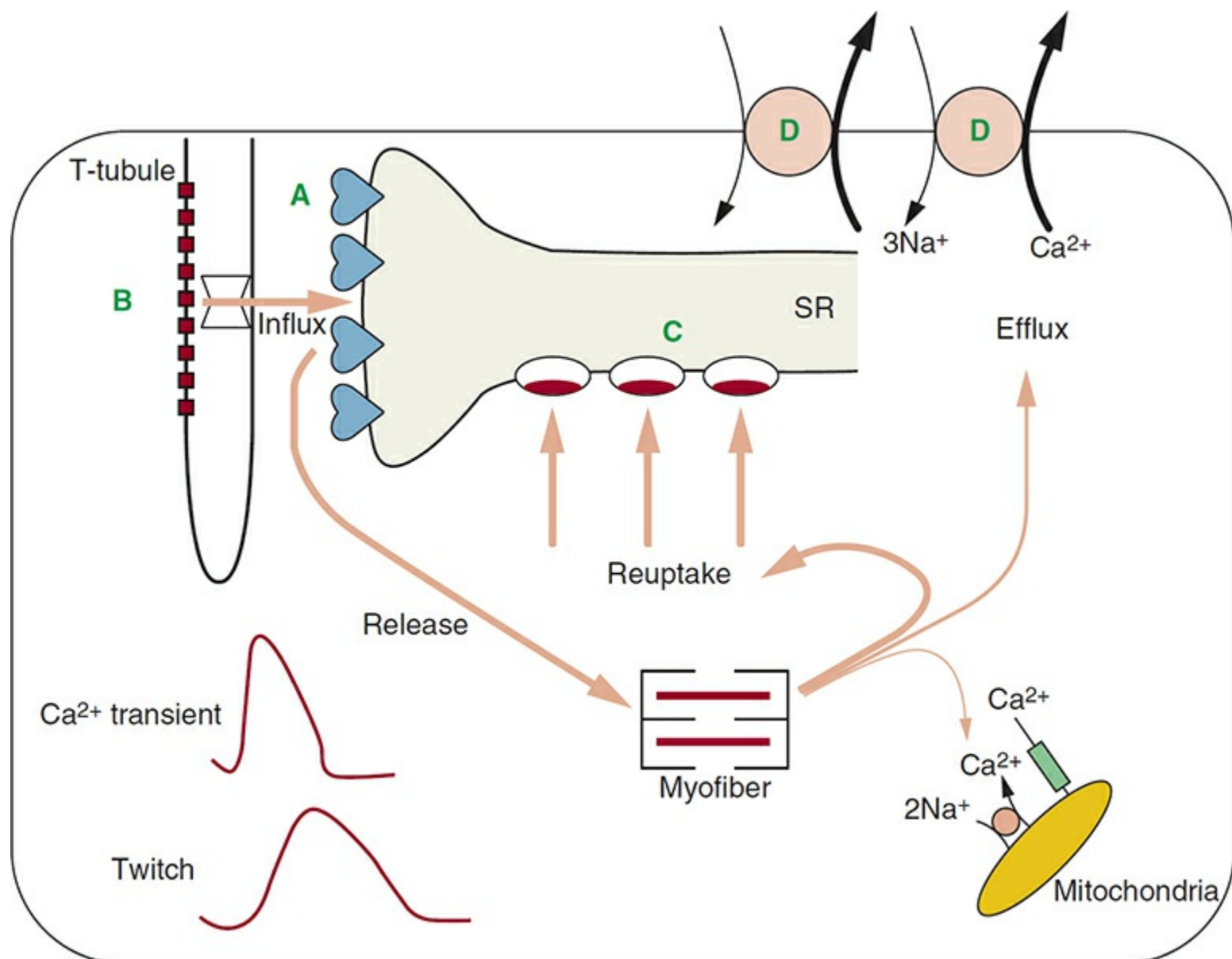


FIGURE 5-2 Major components of excitation–contraction coupling in cardiomyocytes. (Adapted with permission from Scoote M, Poole-Wilson PA, Williams AJ, et al. The therapeutic potential of new insights into myocardial excitation-contraction coupling. *Heart*. 2003 Apr;89(4):371-376.)

5-3. A 54-year-old woman was recently started on furosemide for pedal edema related to prolonged standing. Shortly after starting furosemide, she feels fatigued and confirms dizziness with standing. Her past medical history is notable for hypertension that had not been treated. Her blood pressure is 158/82 sitting and her heart rate is 85. Her physical exam is notable for flat neck veins, a nondisplaced apical impulse, and a soft S4. Which of the following is *not true* for this patient?

- A. Discontinuation of her diuretic and increased fluid intake would increase the peak tension in her cardiac muscle fibers following muscle contraction
- B. Increasing preload through hydration would increase cardiac output, in part by the increased sensitivity to calcium by myofilaments at longer sarcomere lengths
- C. Increased heart rate would result in faster cardiac relaxation
- D. Increasing afterload would increase myofilament shortening velocity
- E. A cup of coffee could increase contractility

5-4. Which of the following is *true* regarding the cardiac cycle?

- A. The *c* wave occurs during isovolumic contraction
- B. The *v* wave occurs just after the QRS complex on the ECG, but before the T wave
- C. The change in ventricular pressure during ventricular filling is a property of ventricular stiffness
- D. Ventricular stiffness is constant during contraction and relaxation
- E. The area enclosed within the pressure–volume loop (PVA) is proportional to myocardial oxygen consumption

Questions 5-5 through 5-7 relate to the following vignette.

A 54-year-old woman is brought to the catheterization laboratory to assess her hemodynamics for shortness of breath. A precatheterization echocardiogram revealed normal ventricular function. Moreover, her filling pressures are normal.

5-5. Which of the following is *not true* regarding ventricular function?

- A. A modest volume challenge would be expected to increase stroke volume
- B. Left ventricular (LV) compliance is determined entirely by the intrinsic elastic properties of the left ventricle
- C. A bolus of norepinephrine would be expected to decrease the velocity of LV shortening
- D. The rate of LV pressure development (dP/dt) is dependent on preload but relatively independent of afterload
- E. Increasing the heart rate from 80 to 95 is unlikely to increase cardiac output

5-6. Which of the following is *true* regarding her diastolic function?

- A. Ventricular relaxation is energy-independent
 - B. Tau, the time constant of LV relaxation, is increased with β -adrenergic receptor stimulation
 - C. The end-diastolic pressure–volume relationship is influenced by changes in intrathoracic pressure, pericardial constraint, and ventricular interaction
 - D. The sarcomeric protein titin does not meaningfully contribute to diastolic function
 - E. The PV relationship during systole reflects the lusitropic state of the heart
- 5-7. Right heart catheterization revealed a right atrial pressure of 5 mm Hg, a right ventricular (RV) pressure of 25/5 mm Hg, a pulmonary artery (PA) pressure of 25/10 mm Hg, and a wedge pressure of 10 mm Hg. The aortic pressure was 120/85 mm Hg, and heart rate was 85. The cardiac output was calculated to be 6 L/min. Which of the following is correct?
- A. The mean arterial pressure (MAP) is 108 mm Hg
 - B. The mean PA pressure is 15 mm Hg
 - C. The systemic vascular resistance (SVR) is 14.5 Wood units
 - D. The pulmonary vascular resistance (PVR) is 2.5 Wood units
 - E. None of the above
- 5-8. Which of the following is *true* about the coronary circulation?
- A. Collateral vessels around a coronary obstruction have myocardial blood flow during exercise similar to that of the native coronary artery
 - B. To meet the increased oxygen demands during exercise, the myocardium dramatically increases its extraction of oxygen from the blood
 - C. Adenosine is a major mediator of coronary autoregulation
 - D. Coronary vascular resistance is greater in the subendocardial coronary circulation than in the subepicardial coronary circulation
 - E. The principal endothelial derived relaxing factor is adenosine
- 5-9. Which of the following is *true* about control of the circulation?
- A. Arterial pressure regulation is controlled primarily by the parasympathetic nervous system
 - B. One result of carotid baroreflex resetting is increased receptor firing for a given mean arterial blood pressure
 - C. The Bezold–Jarisch reflex occurs with a decrease in ventricular distension and results in bradycardia and hypotension
 - D. Endothelins constrict arterioles and decrease preload
 - E. Endocannabinoids increase contractility
- 5-10. With reference to the venous return curves in Figure 5-3, which of the following is *incorrect*?

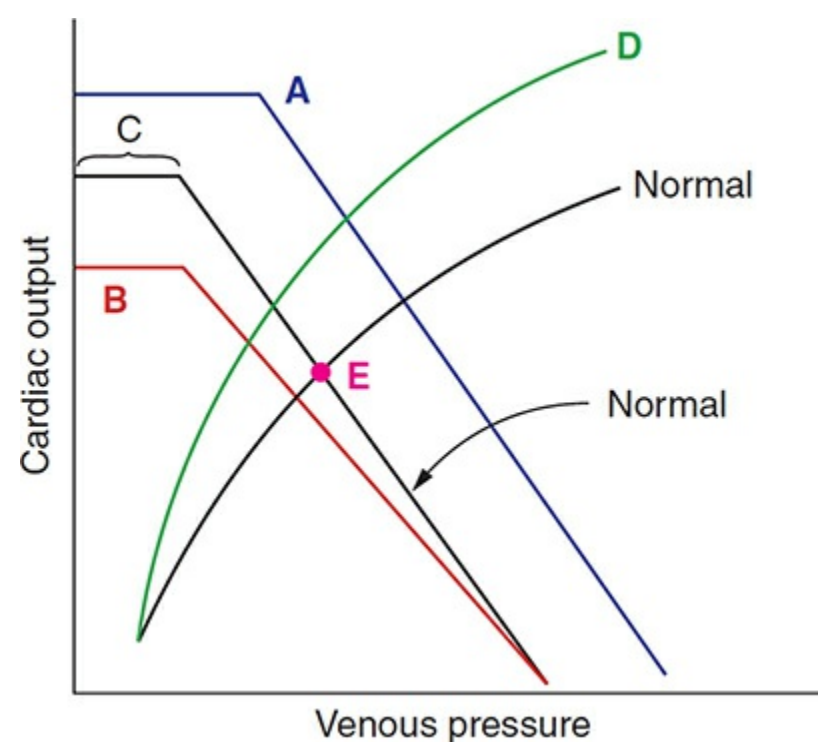


FIGURE 5-3 Venous pressure–cardiac output return curve.

- A. Line A is the effect of volume loading or increasing venous pressure
- B. Line B is the effect of arteriolar vasodilation
- C. The flat portion of the curve in C represents the maximal cardiac output as venous return is reduced
- D. The shift in the Frank–Starling curve to curve D is the effect of increased sympathetic tone
- E. Point E is the equilibrium point where the ability of the venous system to provide enough return at a given pressure is matched by the ventricle’s ability to pump that return when distended to that pressure

ANSWERS

- 5-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 5*). Cardiomyocytes are specialized cells that couple membrane depolarization with cellular contraction. Phase 1 depolarization is the result of sodium influx through Na^+ channels. Sodium influx is *regenerative*, in that increasing membrane depolarization opens more Na^+ channels (option A). Rapid depolarization is limited by K^+ efflux but also by the closure of inactivation gates on Na^+ channels that prevent reopening of individual channels only after the membrane has been fully repolarized (option B). The phase 2 plateau is the result of balanced K^+ efflux and Ca^{2+} influx through L-type Ca^{2+} channels (option C). Phase 3 repolarization is the result of K^+ efflux primarily through the delayed outward K current (I_K). The funny current (I_F) is a specialized channel found in pacemaker cells that results in spontaneous depolarization of the cell during phase 4 and in automaticity (option D). Phase 4 occurs during diastole and requires the Na^+/K^+ ATPase to restore and maintain low intracellular Na^+ and high intracellular K^+ concentrations (option E).
- 5-2. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 5*). In [Figure 5-2](#), channel A is the ryanodine receptor on the sarcoplasmic reticulum (SR). Channel B is the L-type Ca^{2+} channel on the sarcolemma. Channel C is the SERCA pump on the sarcoplasmic reticulum, and channel D is the $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) on the sarcolemma. Calcium uptake and calcium release is the result of calcium release from the SR through the ryanodine receptor (A) after calcium influx into the cell through the L-type Ca^{2+} channel (B) (option A). The calcium transient is a result of (1) Ca^{2+} influx through the L-type Ca^{2+} channel and the *reverse mode* NCX; (2) the amount of calcium in the SR; (3) the amount of calcium released by the SR for a given calcium current; and (4) intracellular Ca^{2+} buffers. NCX can operate in the reverse mode during cellular depolarization, when the intracellular Na^+ content is high. The net effect is Na^+ extrusion and Ca^{2+} uptake. This is a minor contribution to the calcium transient (option B). The calcium transient declines largely because the SERCA ATPase sequesters calcium into the SR. This requires ATP and is energy-dependent (option C). Calcium concentrations are coupled to contraction. Calcium-bound TnC essentially pulls TnI off actin. Thus, TnI can no longer inhibit the formation of myosin-actin crossbridges (option D).
- 5-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 5*) Options A and B reflect the Frank-Starling mechanism. A key property of healthy cardiac muscle is faster relaxation times with increasing heart rates (option C). This occurs by increased SERCA activity as a result of phospholamban phosphorylation. By the force-velocity relationship, the initial velocity of shortening is inversely related to afterload (option D). Caffeine is a calcium sensitizer and can result in an increased force of contraction (option E).
- 5-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 5*) The *c* wave is the result of increased atrial pressure as the mitral valve bulges into the atrium during isovolumic contraction (option A). The *v* wave occurs as the atrium fills during ventricular systole and atrial pressure falls with mitral valve opening. The *v* wave occurs after the T wave (option B). During ventricular filling, change in ventricular pressure is a function of ventricular compliance (option C). Isolated, perfused hearts have been instrumental in the development of our understanding of ventricular mechanics. These models have allowed for the determination that ventricular elastance increases during ventricular contraction and decreases with ventricular relaxation (option D). The PVA is proportional to the myocardial oxygen consumption but includes the area within the PV loop as well as the area between the end-systolic pressure relation and the end-diastolic P-V relation (option E).
- 5-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 5*) The woman in the vignette has a normal right heart catheterization and likely is short of breath for noncardiac reasons. Increasing preload is expected to increase stroke volume (option A). LV compliance *in vivo* is determined by pericardial pressure, right ventricular pressure and volume, coronary artery perfusion, and the intrinsic elastic properties of the LV (option B). An increase in afterload, such as with a bolus of norepinephrine, is expected to decrease stroke volume and the velocity of LV shortening (option C). Changes in heart rate from 60 to 160 beats per minute are unlikely to increase cardiac output because the small increase in contractility is offset by the decrease in diastolic filling time and the resulting preload (option E).
- 5-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 5*) Ventricular relaxation is an energy-dependent process requiring ATP for SERCA sequestration of calcium into the sarcoplasmic reticulum, among other processes (option A). β -adrenergic stimulation leads to the activation of PKA and the phosphorylation of phospholamban, resulting in increased SERCA activity. Increased SERCA activity results in faster relaxation, and a decrease of Tau (option B). Chamber stiffness is affected by intrinsic LV factors and extrinsic factors such as pericardial constraint, atrial contraction, intrathoracic pressures, and ventricular interaction (option C). In addition to active relaxation, diastolic function is also related to the viscoelastic properties of the LV. LV recoil is affected by titin and the extracellular matrix (option D). The P-V relationship during diastole reflects the lusitropic state of the heart (option E).
- 5-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 5*) The MAP is $(120 + 2 * 85)/3 = 97$ (option A). The PA pressure is $(25 + 2 * 10)/3 = 15$ (option B). SVR is $(97 - 5)/6 = 15.33$ Wood units (option C). The PVR is $(15 - 10)/6 = 0.83$ Wood units (option D).

- 5-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 5*) Collateral vessels that become prominent with obstructive coronary disease cannot augment coronary flow similar to that of the native artery with stress or exercise (option A). Unlike skeletal muscle, the myocardium operates at nearly peak oxygen extraction at rest. Increased oxygen needs are met by increases in blood flow through the coronary circulation (option B). Adenosine levels increase with the breakdown of ATP, and adenosine is a potent coronary vasodilator. If coronary blood flow decreases, local adenosine levels increase, making adenosine an integral component of coronary autoregulation (option C). To maintain equal coronary flow throughout the myocardium, the subendocardial vessels have less resistance than the subepicardial vessels. This is important because subendocardial vessels have a limited ability to further vasodilate in time of stress, and subendocardial zones are more prone to ischemia (option D). The principal endothelial derived relaxing factor is nitric oxide (NO) (option E).
- 5-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 5*). Parasympathetic nerves supply only a small portion of the resistance in vessels; the sympathetic nervous system is the primary regulator of vascular resistance (option A). Carotid baroreflex resetting results in decreased receptor firing for a given mean arterial blood pressure (option B). The Bezold–Jarisch reflex is mediated by ventricular C fibers, which are activated by hypovolemia. The net result is a paradoxical bradycardia and hypotension (option C). Endothelin constricts arterioles and venules. The effect on venules serves to increase preload (option D). Endocannabinoids decrease contractility (option E).
- 5-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 5*). The venous return curve describes the relationship of cardiac output and venous pressure. Volume loading or venoconstriction shifts the curve up and to the right (option A). By contrast, arteriolar vasoconstriction shifts the curve down and to the left (option B). The flat portion of the curve in C represents the maximal cardiac output as venous return is reduced (option C). The Frank–Starling curve describes the effect of ventricular loading with cardiac output and moves up and to the left at higher levels of contractility (option D). The intersection of the Frank–Starling curve and the venous return curve represents the equilibrium point of venous return and ventricular performance (option E).

CHAPTER 6

Molecular and Cellular Biology of the Heart

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 6-1.** A 55-year-old man presents with exertional dyspnea and a 10 lb weight gain. His physical exam is notable for an elevated jugular venous pressure, a soft apical holosystolic murmur, and an S3 gallop. Echocardiography reveals a dilated left ventricle with an ejection fraction of 35%. Which of the following is most likely *true* regarding β -adrenergic signaling in this patient?
- A. β 2-adrenergic receptors (β 2-AR) are the dominant type of β -adrenergic receptor in the heart
 - B. An increase in GRK2 activity contributes to β -adrenergic receptor desensitization
 - C. β 1-AR density is increased in this patient's myocytes
 - D. This patient's heart is more sensitive to β -agonists now than before developing decompensated heart failure
 - E. β 1-AR signaling is likely to protect against apoptosis in his cardiomyocytes
- 6-2.** Which of the following is *incorrect* regarding excitation–contraction coupling?
- A. Depolarization of the cardiomyocyte membrane results in the opening of L-type calcium channels
 - B. The SERCA ATPase functions to sequester calcium in the sarcoplasmic reticulum during relaxation
 - C. In a healthy heart, tachycardia results in decreased calcium in the cytoplasm of the cardiomyocyte and increased contractile force
 - D. PKA and CaMKII maintain SERCA activity by phosphorylating and inactivating phospholamban
 - E. The efficiency of the ryanodine receptor response to cytoplasmic calcium is dependent on the ryanodine receptor's proximity to the L-type calcium channel
- 6-3.** A 54-year-old patient with a history of heart failure with reduced ejection fraction is admitted following 3 shocks from his internal cardiac defibrillator. Which of the following could contribute to a proarrhythmic state in this patient?
- A. Hyperphosphorylation of the ryanodine receptor contributes to a calcium leak from the sarcoplasmic reticulum
 - B. Increased systolic calcium concentrations in myocytes
 - C. An increased force-frequency relationship
 - D. A shortened relaxation phase
 - E. Increased SERCA expression and activity
- 6-4.** Which of the following is *not true* regarding signaling pathways in heart failure?
- A. An increased intracellular concentration of calcium leads to increased activity of calcineurin in failing myocytes
 - B. CaMKII contributes to hypertrophy by phosphorylating transcription factors such as MEF2 and class II histone deacetylases
 - C. Prohypertrophic growth factors tend to work through heterotrimeric proteins of the Gq family
 - D. Mechanical stretch alone can induce many hypertrophic signaling pathways
 - E. Hallmarks of a fetal-gene expression program during hypertrophy include the expression of BNP, ANF, and α -MHC

Questions 6-5 through 6-7 refer to the following vignette.

A 52-year-old man presents to your office for a follow-up appointment. He has a long-standing history of hypertension. His ECG is suggestive of left ventricular hypertrophy, and his echocardiogram shows a left ventricular wall thickness of 1.4 cm.

- 6-5.** Which of the following is *not true* regarding signaling pathways in this patient?
- A. Protein synthesis is dramatically upregulated through the PI3K and mTOR pathways
 - B. Extracellular signal-related kinases (ERKs) are activated
 - C. GSK-3 β activity is reduced in cardiomyocytes undergoing hypertrophic growth

- D. Hypertrophic signaling has a strong overlap with factors known to broadly regulate organ size
E. mTORC1 has an important role in pathologic, but not physiologic hypertrophy
- 6-6.** Which of the following is *not true* regarding microRNA signaling in this patient?
- A. The miR212/132 family of microRNAs promotes hypertrophy by the inhibition of the antihypertrophic transcription factor FoxO3
B. MiR-133 levels are increased and promote hypertrophy and fibrosis
C. Anti-miRs are an approach to pharmacologically modulate microRNA signaling
D. MiRs that promote myocardial glucose utilization are investigational approaches to prevent the progression to heart failure
E. Exosomes secreted from the heart allow for the systemic circulation of miRNAs to other organ beds
- 6-7.** Which of the following is *true* regarding lncRNAs in this patient?
- A. The lncRNA CHAST is likely to be upregulated
B. LncRNAs, by definition, are not translated into protein products
C. LncRNAs exert their effects solely through the inhibition of complementary transcripts
D. LncRNAs are found only in intergenic regions
E. LncRNAs are highly conserved across phyla
- 6-8.** Which of the following is *not true* regarding cell death in the development of heart failure?
- A. Cytochrome C release marks cells about to undergo necrotic cell death in the failing heart
B. Prolonged ER stress can trigger cell death pathways
C. Apoptotic cell death is programmed cell death that does not typically result in an inflammatory response
D. Necrotic cell death is marked by a loss of membrane integrity, extrusion of intracellular contents, and inflammation
E. Apoptotic cell death is energy dependent, but necrotic cell death is energy independent
- 6-9.** Which of the following is *not true* regarding cardiac fibroblasts?
- A. Cardiac fibrosis is the result of collagen production in excess of collagen degradation
B. Cardiac fibroblasts differentiate into myofibroblasts that express contractile proteins
C. The main components of cardiac extracellular matrix are proteoglycans and elastin
D. Pathologic cardiac fibrosis is proarrhythmogenic, in part, because of electrical isolation of regions of the myocardium
E. Cardiac fibroblasts in the adult heart are primarily derived from resident fibroblasts
- 6-10.** Which of the following is *true* regarding cardiac microRNAs?
- A. The majority of transcripts in the genome encode proteins
B. MicroRNAs, PIWI-interacting RNAs, and endogenous short interfering RNAs are types of long ncRNAs
C. MiRNAs regulate gene expression by binding to mRNAs, resulting in degradation
D. The number of ncRNAs decreases with increasing complexity of the species
E. Long ncRNAs are more than 2000 base pairs long

ANSWERS

- 6-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 6*) This patient presents with classic findings of heart failure with reduced ejection fraction. In the normal heart, 60% to 80% of β -adrenergic receptors are of the β 1 subtype.¹ With heart failure, β 1-AR is downregulated, and the β 1-AR/ β 2-AR ratio nearly normalizes (options A and C).² A molecular hallmark of heart failure is the desensitization of the β -adrenergic signaling axis. A failing heart is less sensitive to exogenous β -AR ligands than is a normal heart (option D). At the molecular level, this occurs by a decreased density of β 1-AR in cardiomyocytes and increased levels of GRK2. GRK2 phosphorylates β -ARs and reduces their sensitivity (option B).³ Chronic β -AR signaling through the β 1-AR is believed to contribute to cardiomyocyte apoptosis seen in heart failure (option E).³
- 6-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 6*) Following depolarization of the cardiomyocyte membrane, L-type calcium channels open, and calcium influxes into the cardiomyocyte (option A).⁴ In response, ryanodine receptors release calcium from the sarcoplasmic reticulum. The net result is an increase in cytoplasmic calcium that leads to increased myofilament contractility. Activation of ryanodine receptors is more efficient when they are in close proximity to the calcium influx through L-type calcium channels (option E).⁵ An increase in force with increasing heart rate is due to increased cytoplasmic calcium and is known as the force-frequency relationship (option C). The force-frequency relationship is an important feature of the healthy heart. During relaxation, cytoplasmic calcium is sequestered in the

sarcoplasmic reticulum by the SERCA ATPase (option B). SERCA activity is negatively regulated by phospholamban.^{6,7} PKA and CaMKII can phosphorylate and inactivate phospholamban, thus maintaining SERCA activity (option D).

- 6-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 6*) Intracellular calcium homeostasis is altered in the failing cardiomyocyte. Hallmarks of the failing cardiomyocyte include (1) decreased systolic calcium, (2) increased diastolic calcium, and (3) a prolonged relaxation phase (options B and D).⁴ Additionally, the force-frequency relationship is altered such that contractile force decreases with increasing heart rate (option D). Biochemically, the L-type calcium channel does not activate the ryanodine receptor as efficiently, and hyperphosphorylation leads to an increased sensitivity of the ryanodine receptor.⁸ Calcium leak from the ryanodine receptor can result in delayed afterdepolarizations, an important contributor to arrhythmogenesis (option A).^{4,9} Finally, SERCA expression has been demonstrated to be reduced in animal and human models of heart failure, and the restoration of normal SERCA levels has been a focus of gene therapy efforts for patients with heart failure (option E).^{7,8}
- 6-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 6*) Hypertrophic signaling results from complex inputs at the membrane and within the cell. Mechanical stretch alone can activate many of the signaling pathways involved in hypertrophy through surface-bound integrins and mechanically activated ion channels (option D).¹⁰ Additionally, prohypertrophic growth factors such as angiotensin II work through heterotrimeric G-proteins (option C). The Gq family is particularly important because overexpression of Gq is sufficient to cause hypertrophy.¹¹ A key feature of hypertrophic signaling is an increase in intracellular calcium that binds to calmodulin, resulting in the activation of calcineurin and CaMKII (option A). Both calcineurin and CaMKII lead to the activation of transcription factors that promote hypertrophic gene expression programs. CaMKII activates the transcription factors MEF2 and HDAC2 by phosphorylation (option B).¹² One result of hypertrophic signaling is re-expression of factors from cardiac development, such as BNP, ANF, and β -MHC (option E).¹³
- 6-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 6*) Hypertrophic cardiomyocytes have dramatic upregulation of protein synthesis via the PI3K and mTORC pathways (option A). Many stimuli that result in cardiac hypertrophy also activate PI3K signaling. mTORC1 signaling is one example of several growth pathways that are activated with cardiac hypertrophy. mTORC1 appears to be broadly related to cardiac growth as inhibition compromises both physiologic and pathologic hypertrophy (options D and E).¹⁴ Additionally, MAPK activity is thought to be increased and GSK-3 β activity reduced during hypertrophy (option C).¹⁵
- 6-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 6*) The importance of microRNA signaling to the pathologic hypertrophy and the progression of heart failure is being increasingly recognized. MicroRNAs regulate multiple processes, such as hypertrophic signaling pathways, tissue fibrosis, vascular density, and cardiac metabolism (option D).¹⁶ MiR-133 is downregulated with cardiac stress and has protective effects against hypertrophy and tissue fibrosis (option B).¹⁷ By contrast, miR212/132 are increased with cardiac stress and promote hypertrophic signaling by repressing the antihypertrophic transcription factor FoxO3 (option A).¹⁸⁻²⁰ MicroRNAs are promising therapeutic targets and can be specifically targeted by modified nucleic acids that function as anti-miRs (option C). Finally, the systemic roles of cardiac microRNAs are being increasingly understood because cardiac microRNAs can be found in the circulation within small vesicles called exosomes (option E).²¹
- 6-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 6*) LncRNAs were originally defined as noncoding RNAs greater than 200 base pairs in length.²² LncRNAs can be found within coding genes and intergenic regions (option D). LncRNAs have emerged as complex molecules with a diverse set of regulatory functions.²³ They can repress transcription by binding transcripts, and they directly interact with proteins to regulate their function (option C). More recently, some lncRNAs have been identified that encode small proteins, such as the protein DWORF that activates the SERCA pump (option B).²⁴ LncRNAs tend to be poorly conserved across phyla (option E). The lncRNA CHAST is an exception, and elevations have been identified in murine models of pressure overload and in hypertrophied human heart tissue (option A).²⁵
- 6-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 6*) Cardiomyocyte cell death is an important contributor to the progression to heart failure. Cell death can occur via necrotic cell death following injuries to the heart or programmed apoptotic cell death. Necrotic cell death is an energy independent process that is marked by a loss of membrane integrity, resulting in extrusion of intracellular contents and inflammation (option D).²⁶ Apoptotic cell death, by contrast, is programmed and triggered by both intracellular and extracellular stimuli (options C and E). For example, prolonged ER stress can lead to the triggering of death pathways (option B). In failing hearts, some myocytes exhibit features of apoptotic cell death, such as mitochondrial cytochrome C release, but they can survive and maintain intact nuclei (option A).²⁷ These cells are thought to undergo reversible damage.
- 6-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 6*) In response to stress, the heart undergoes pathologic remodeling, with proliferation of resident fibroblasts to make more fibroblasts (option E).²⁸ These fibroblasts tip the balance of extracellular matrix turnover toward excess production compared to degradation (option A).^{28,29} Extracellular matrix is a complex network of collagens, elastin, glycoproteins, and proteoglycans. However, type I collagen is the main component (option C).³⁰ Cardiac fibrosis stiffens the heart and can be proarrhythmic by electrically isolating parts of the

myocardium (option D).^{31,32} In addition to roles in maintaining the balance of cardiac extracellular matrix, cardiac fibroblasts can differentiate into myofibroblasts that express contractile proteins. Myofibroblasts play important roles in contracting the wound following injury (option B).³³

- 6-10. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 6*) As a result of widespread sequencing, the vast number of ncRNAs has been recognized. It has now been determined that although about three-fourths of the mammalian genome is transcribed, less than 2% is ultimately translated into proteins (option A).³⁴ Short ncRNAs are < 200 bp in length and include microRNAs, PIWI-interacting RNAs, and endogenous short interfering RNAs. By contrast, long ncRNAs are longer than 2 kb in length (options B and E).³⁵⁻³⁸ MiRNAs can repress gene expression by binding to target mRNAs, resulting in degradation (option C). MiRNAs are increasingly recognized as important regulators of gene expression and cell identity. The number of ncRNAs increases with increasing organism complexity (option D).³⁹

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CHAPTER 7

Biology of the Vessel Wall

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

7-1. Which of the following is *true* about vascular development?

- A. A bipotent hemangioblast is capable of giving rise to endothelial cells and blood cells
- B. The primitive vasculature arises from coalesced blood islands
- C. Postnatal vasculogenesis requires angioblasts that are active in the adult
- D. Collateral arteries that form in the presence of obstructive coronary artery disease are the result of bone-marrow-derived progenitor cells
- E. VEGF is a potent inhibitor of angiogenesis

7-2. Which of the following is *incorrect* regarding the role of endothelial cells?

- A. The endothelium serves as a prothrombotic surface
- B. The endothelium regulates the inflammatory response by affecting leukocyte recruitment and margination
- C. The endothelium helps to regulate vascular tone
- D. The endothelium regulates signaling by allowing for the selective passage of molecules across the barrier
- E. The endothelium serves as a barrier to circulating blood constituents

7-3. Which of the following is *not true* about signaling in endothelial cells?

- A. Inflamed endothelium produces tissue factor, which creates a procoagulant surface
- B. Water-soluble molecules are transported across the endothelium via caveolae
- C. L-selectin, P-selectin, and VCAM-1 are important to the capture of leukocytes by the endothelium during inflammation
- D. NO acts as a vasoconstrictor by increasing levels of cGMP, which reduces intracellular calcium concentrations and results in the dephosphorylation of MLCK in smooth muscle
- E. PGI₂ is made by the endothelium and promotes vascular relaxation by increasing cAMP levels in smooth muscle cells

7-4. Which of the following *do not* promote the conversion of vascular smooth muscle to a synthetic phenotype?

- A. PDGF
- B. FGF
- C. TGF- β
- D. NO
- E. IGF-1

7-5. Which of the following is *not true* regarding the vascular extracellular matrix (ECM)?

- A. Degradation of the ECM is one of the earliest events during angiogenesis
- B. Matrix metalloproteinases degrade the ECM
- C. Increased MMP activity has been noted in abdominal aneurysms
- D. Increased MMP activity is found in the shoulder of an atherosclerotic plaque
- E. Secreted MMPs are inactivated by plasmin

7-6. Which of the following is *not* a characteristic of endothelial dysfunction?

- A. Endothelial dysfunction is associated with cardiovascular risk factors such as diabetes, smoking, and a family history of atherosclerotic disease
- B. A hallmark of dysfunctional endothelium is increased NO production
- C. Dysfunctional endothelium recruits monocytes and macrophages to the vessel wall

- D. Endothelial dysfunction precedes the morphological presence of atherosclerotic plaque
E. All of the above
- 7-7.** A 64-year-old man is admitted with an anterior ST elevation myocardial infarction. He is taken to the cardiac catheterization laboratory and undergoes successful percutaneous intervention with a drug-eluting stent. Which of the following is *not true* regarding the stent?
- A. Drug-eluting stents inhibit intimal smooth muscle proliferation
B. Smooth muscle proliferation is the cause of in-stent restenosis
C. Restenosis occurs in 5% to 10% of older generation drug-eluting stents
D. Newer generation drug-eluting stents with thicker struts and improved drug delivery have worse reendothelialization than older drug-eluting stents
E. None of the above
- 7-8.** Which of the following is *true* about vascular progenitor cells?
- A. Endothelial progenitor cells are found only in the bone marrow
B. Pericytes share properties with mesenchymal stem cells
C. Adventitial stem cells give rise to cardiomyocytes
D. Vascular smooth muscle progenitors, unlike other smooth muscle cells within the vascular wall, are proliferative
E. B and C
- 7-9.** A 43-year-old woman presents with progressive shortness of breath. Physical exam reveals elevated neck veins, a right ventricular (RV) lift, and a loud P2. Echocardiography shows normal left ventricular function but elevated pulmonary artery pressures. Right heart catheterization shows a normal pulmonary capillary wedge pressure but markedly elevated pulmonary artery pressures. Which of the following is *not true* regarding therapies for pulmonary hypertension?
- A. Epoprostenol, iloprost, and treprostinil result in vasodilation of the pulmonary vasculature
B. Sildenafil and tadalafil cause vasodilation by increasing NO levels
C. Bosentan affects endothelin receptors on smooth muscle cells and endothelial cells
D. Ambrisentan and macicentan are selective ET-A antagonists that inhibit smooth muscle vasoconstriction
E. All of the above are true
- 7-10.** Which of the following is *true* regarding signaling pathways in vascular smooth muscle cells?
- A. IP3 increases cytoplasmic calcium by direct inhibition of SERCA
B. DAG inhibits muscle contraction via PKC
C. The initial phase of smooth muscle contraction is the result of the latch-bridge state
D. Rho activation desensitizes MLC to intracellular calcium
E. None of the above

ANSWERS

- 7-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 7*) The notion that a bipotent hemangioblast gives rise to endothelial cells and blood cells has recently been challenged. Instead, blood cells probably develop from hemogenic endothelial cells residing in specialized vascular niches (option A).¹ Early blood vessels are derived from blood islands, which are clusters of mesodermal progenitor cells. These islands are marked by central hematopoietic progenitor cells and peripheral angioblasts (option B). Unlike during development, postnatal vasculogenesis does not rely on angioblasts, but instead occurs by the sprouting of new vessels from preexisting vessels. In the adult, vasculogenesis may be limited. However, in scenarios such as the development of collateral vasculature with obstructive coronary artery disease, arteriogenesis occurs. Arteriogenesis occurs by the sprouting of new vessels from preexisting capillaries or arterio-arterio anastomoses (option C).² Much work has gone into understanding cytokines that stimulate vasculogenesis. The prototypical angiokine is VEGF.³ In fact, VEGF inhibitors are used clinically as anticancer agents to inhibit tumor-related angiogenesis (option E).
- 7-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 7*) Among its many functions, the endothelium is of particular importance for maintaining and protecting the integrity and function of the vascular wall, with specific roles. These include (1) functioning as a metabolic tissue that actively secretes vasoactive factors governing vascular tone (option C); (2) acting as an anticoagulant and antithrombotic surface (option A); (3) serving as a barrier to most circulating blood constituents (option E); (4) regulating the transendothelial passage of specific molecules, proteins, and cells across this barrier (option D), and (5) participating in the inflammatory response via active leukocyte recruitment and facilitation of leukocyte margination from the lumen into the vessel wall and adjacent tissues (option E).

- 7-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 7*) As a part of its barrier function, the endothelium regulates the transport of molecules from the vascular lumen to tissues. Water-soluble molecules, in particular, are transported across endothelial cells in vesicles called caveolae.⁴ The endothelium generally serves as an antithrombotic surface. However, when inflamed, the endothelium expresses tissue factor, factor VIII, PAI-1, and factor Va, which create a procoagulant milieu (option A).⁵ The endothelium has important roles in regulating inflammation. These include capture, adhesion, and migration of leukocytes (option C).⁶ NO and PGI₂ are vasodilators (options D and E).
- 7-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 7*) Conversion of a vascular smooth muscle cell from a quiescent, differentiated phenotype to a proliferative, synthetic phenotype is a hallmark of pathologic states such as neointimal hyperplasia. Agents such as NO, prostacyclin, and heparin inhibit growth and promote a differentiated phenotype (option D).⁷⁻⁹ By contrast, growth factors such as PDGF, FGF, and IGF-1 promote smooth muscle cell migration and hyperplasia (options A, B, and E).¹⁰ TGF- β can promote either the differentiated or synthetic phenotype, depending on the context (option C).
- 7-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 7*) MMPs are a diverse class of proteins that degrade the ECM (option B). TIMPs antagonize MMPs and stabilize the ECM. MMPs allow for the growth and proliferation of new blood vessels (option A). Importantly, TIMPs and MMPs play a pivotal role in the pathology of atherosclerotic plaques and aneurysms (option C).^{11,12} MMPs are highly expressed in the shoulder regions of atherosclerotic plaques and predispose to plaque rupture (option D).¹³ MMPs can either be membrane-spanning or secreted. Secreted MMPs are secreted as zymogens and are activated after cleavage by plasmin (option E).
- 7-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 7*) Endothelial dysfunction precedes the development of atherosclerotic plaque (option D). Dysfunctional endothelium has an impaired capacity for NO production (option B) and upregulates inflammatory markers that lead to the recruitment of inflammatory cells (option C).^{14,15} These inflammatory cells infiltrate the vessel wall and oxidize LDL, triggering atheroma formation.¹⁶ Endothelial dysfunction has been correlated to many clinical factors associated with coronary atherosclerotic disease (option A).¹⁷⁻¹⁹
- 7-7. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 7*) Percutaneous interventions with balloon angioplasty and bare metal stents were plagued with high rates of restenosis. Acute arterial injury results in smooth muscle proliferation. This proliferation is a major feature of restenosis (option B). Stents eluting antiproliferative drugs prevent smooth muscle proliferation, leading to reduced rates of restenosis (option A). Unfortunately, these drugs also prevented reendothelialization of the stents and are associated with acute stent thrombosis. Newer generation drug-eluting stents, with thinner struts and better drug delivery, are associated with less stent thrombosis and have better reendothelialization (option D). In the contemporary era of drug-eluting stents (DES), clinically significant restenosis arises in only 5% to 10% of treated.
- 7-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 7*) Endothelial progenitor cells (EPCs) expand and proliferate to make new endothelial cells. Recent work has identified a local source of EPCs within the vessel wall (option A).² Pericytes can differentiate into adipocytes, chondrocytes, and osteocytes and share properties with mesenchymal stem cells (option B).^{2,22} Adventitial stem cells are still under investigation but appear to give rise to smooth muscle cells, endothelial cells, and myofibroblasts (option C).²³ The presence of VSMCs in the vessel wall is controversial. Both putative VSMCs and mature SMCs can proliferate (option D).^{24,25}
- 7-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 7*). Epoprostenol, iloprost, and treprostinil are all prostacyclin analogs and result in pulmonary vasodilation (option A).²⁶ Sildenafil and tadalafil inhibit phosphodiesterase and increase cGMP levels, leading to vasodilation. They do not directly increase NO levels (option B).²⁶ Bosentan, ambrisentan, and macitentan are endothelin receptor antagonists. Endothelin causes smooth muscle-mediated vasoconstriction via the ET-A receptor and endothelial cell-mediated vasodilation via the ET-B receptor (option C). Bosentan is a mixed ET-A/ET-B antagonist, but the newer agents ambrisentan and macitentan are more selective for the ET-A receptor (option D).^{26,27}
- 7-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 7*). Vasoactive agents lead to the hydrolysis of phosphoinositides by phospholipase C. As a result, inositol triphosphate (IP₃) and diacylglycerol (DAG) are produced.²⁸ IP₃ binds to IP₃ receptors on intracellular organelles to increase intracellular levels of calcium (option A).²⁹ Increased DAG levels lead to increased PKC activity. PKC works to stimulate contraction in the presence of increased intracellular calcium levels (option B).³⁰ While the initial phase of smooth muscle cell contraction depends on increased intracellular calcium, the sustained phase is related to the latch-bridge state (option C). Essentially, myosin is dephosphorylated when bound to actin. Although the myosin will not actively cycle, it can maintain tension through its association with actin.³¹ The GTPase Rho activates Rho kinase, leading to inactivation myosin phosphatase, type I.³² As a result, MLC remains phosphorylated and is more sensitive to intracellular calcium (option D).³³

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CHAPTER 8

Molecular and Cellular Development of the Heart

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 8-1.** Which of the following is *not true* about the specification of cardiac precursors during gastrulation?
- A. Cardiac precursors are derived from mesoderm following gastrulation
 - B. The fates of cardiac progenitor cells are already determined at the epiblast stage
 - C. The fates of progenitor cells are determined by the sequence and intensity of external signals encountered during gastrulation
 - D. A precursor cell's position within the epiblast determines the complement of external signals it receives
 - E. Mesoderm is the result of epithelial-to-mesenchymal transition (EMT) in the epiblast
- 8-2.** Which of the following is *true* about the specification of mesoderm that gives rise to cardiac cells?
- A. Cells that migrate from the anterior primitive streak give rise to lateral mesoderm
 - B. Cardiac progenitors are found in the lateral plate mesoderm
 - C. The heart and liver are the last mesoderm to be produced by the embryo
 - D. Retinoic acid gradients are important for separating cardiac and forelimb fields, but they do not have a role in determining whether cardiac precursors give rise to atrial cells or ventricular cells
 - E. The first cardiac cells formed in the lateral plate mesoderm are atrial cells
- 8-3.** You see a 2-year-old child for episodes of cyanosis ameliorated by squatting. She is found to have Tetralogy of Fallot. Tetralogy of Fallot most likely results from defects in:
- A. The proliferation of cells in the first heart field
 - B. Fusion of the primordial heart tubes
 - C. The addition of cells from the second heart field to the heart tube
 - D. Cardiac specification during gastrulation
 - E. Specification of atrial and ventricular cardiomyocytes
- 8-4.** Which of the following is *not true* about signaling pathways during cardiac development?
- A. Increased levels of nodal and canonical Wnt signaling promote cardiac specification of pluripotent stem cells to cardiac progenitors
 - B. Endoderm-derived BMP2 promotes the differentiation of cardiac mesoderm to cardiomyocytes
 - C. Noncanonical Wnt signaling restricts the differentiation of cardiac progenitors to cardiomyocytes, but canonical Wnt signaling promotes cardiac differentiation
 - D. Both cardiac progenitors and differentiated cardiomyocytes are equally proliferative
 - E. The differentiation and expansion of the second heart field occurs by a fine balance of canonical Wnt signaling, Notch signaling, and BMP signaling
- 8-5.** Which of the following is *true* about the transcriptional control of cardiac differentiation?
- A. Tbx5 is present mostly in cells from the second heart field
 - B. Pitx2 is important to anterior-posterior patterning
 - C. Nkx2.5, in coordination with Isl1, regulates the differentiation of cardiac progenitors to cardiomyocytes
 - D. Association of p300/CBP with cardiac transcription factors leads to histone deacetylation and the activation of transcription
 - E. Tissue-specific variants of chromatin complexes are not essential to cardiac differentiation
- 8-6.** Which of the following is *true* about cardiac chamber morphogenesis?

- A. The fetal heart begins to approximate the morphology of the adult heart by 6 weeks
 - B. Cardiac jelly is secreted by the endocardium and prevents blood flow until the valves are functional
 - C. Tbx2 and 3 are required for chamber maturation, whereas Tbx20 represses chamber maturation
 - D. Chamber formation and proportion are unrelated to localized regions of proliferation
 - E. Noncompaction results from the lack of the trabecular myocardium to be packed into the compact myocardium
- 8-7.** A 67-year-old woman presents with right-sided hemiparesis. During her evaluation, she is noted to have a patent foramen ovale (PFO). Which of the following is *true* about atrial septation and her PFO?
- A. Her foramen primum failed to close
 - B. Her septum primum did not migrate properly
 - C. Her septum primum and septum secundum failed to fuse
 - D. Her left sinus venosus remains linked to her left atrium
 - E. Her membranous ventricular septum failed to develop
- 8-8.** An infant presents within 1 week of birth with poor feeding, intermittent cyanosis, and respiratory distress. Her exam is notable for a hyperdynamic precordium, bounding peripheral pulse, and a single S2. Echocardiography reveals a diagnosis of truncus arteriosus. Which of the following is *true* about cardiac development in this patient?
- A. Failure to form a truncus could result from defects in neural crest migration or in second heart field precursors
 - B. There is persistence of the fifth pair of aortic arch artery pairs
 - C. The left sixth branchial arch artery failed to give rise to the trunk of the pulmonary artery
 - D. There is persistence of the right sixth branchial arch artery
 - E. There is persistence of the ductus arteriosus
- 8-9.** Which of the following is *not true* of the epicardium?
- A. The epicardium is a mesothelial sheet that covers the heart and has epithelial properties
 - B. The epicardium is multipotent with contributions to cardiac endothelium, fibroblasts, and coronary artery smooth muscle cells
 - C. In the adult heart, the epicardium is inert
 - D. The epicardium arises from the coelomic epithelium, which forms the proepicardium
 - E. The epicardium is a heterogeneous group of cells
- 8-10.** Which of the following is *true* about cardiac development and homeostasis?
- A. Cardiomyocyte renewal does not occur in the adult heart
 - B. The SA node has contributions from both the first and second heart fields
 - C. Cardiac innervation occurs independently of coronary vasculogenesis
 - D. The coronary endothelium has a single source of cells
 - E. Purkinje cardiomyocytes have more mitochondria than other cardiomyocytes in the ventricle

ANSWERS

- 8-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 8*) After gastrulation, the cardiogenic area, containing cardiac precursors, is formed by early gastrulating mesoderm (option A). It is located within the mesodermal component of the splanchnopleural layer of the anteriormost lateral plate.^{1,2} Mesoderm itself is formed by EMT of cells at the central-posterior position in the epiblast (option E).³ Although different regions of the epiblast give rise to specific cell types, the fates of the precursor cells themselves at this stage are not yet determined (option B).⁴ Transplantation studies have shown, for example, that epiblast regions fated to produce brain transplanted to the cardiac-forming region will form the heart, and vice versa. Ultimately, the history of external signals cells receive during their journey through gastrulation determines the differentiation pathway of precursor cells (option C). The sequence of signals received is determined by the location of precursor cells within the epiblast (option D).³
- 8-2. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 8*) Cells migrate out of the primitive streak, such that the anteriormost cells form the axial mesoderm and the posterior cells form the lateral mesoderm (option A). The cardiac fields are found in the lateral plate mesoderm, and along with the hepatic mesoderm they are among the first types of mesoderm specified (options B and C). The first cardiac mesoderm specified gives rise to the septum transversus (option E). Like with gastrulation, local signaling gradients drive differentiation. Retinoic acid gradients, in particular, have been shown to contribute to the separation of cardiac and forelimb fields in addition to the specification of subtypes of cardiac cells, such as atrial and ventricular cardiomyocytes (option D).⁵

- 8-3. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 8*) Tetralogy of Fallot is classically characterized by pulmonary atresia, a VSD, an overriding aorta, and right ventricular hypertrophy. Following cardiac specification in the lateral plate mesoderm, two heart fields emerge (options D and E). The first heart field gives rise to the left ventricle and most of the atria (option A). The second heart field is adjacent to the first heart field and gives rise to the right ventricle, the outflow tract, and parts of the atria and inflow tract.^{2,6,7} Cells from the first heart field differentiate and contribute to the primitive heart tubes (option B). Cells from the second heart tube differentiate somewhat later and are sequentially added. In humans and chicks, there are two primordial heart tubes that must fuse at the midline to form a single heart tube.^{8,9} Defects observed in tetralogy of Fallot are associated with structures derived primarily from the second heart field (option C).
- 8-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 8*) Pluripotent cells are fated to cardiac progenitors by canonical Wnt signaling (option A).^{2,10} As cardiac mesoderm, cardiac progenitors differentiate into cardiomyocytes in response to BMP signaling from the extraembryonic tissues and endoderm adjacent to cardiac mesoderm (option B).¹ Progenitor cells are proliferative and tend to expand to cardiac fields, while differentiated cells are less proliferative (option D). In general, canonical Wnt/FGF/Shh signaling promote the specification of cells to cardiac progenitors, while BMP and noncanonical Wnt signaling promote differentiation into cardiomyocytes (options C and E).^{10,11}
- 8-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 8*) The molecular regulation of cardiomyocyte specification and differentiation has been the subject of intense study. Different transcription factors are important to regional specification of the heart. For example, Tbx5 is present in anterior heart field cells (option A), Hand2 in second heart field cells, and Tbx1 in cells of the outflow tract.^{12,13} More broadly, Gata, Nkx, and Isl factors are important for cardiomyocyte identity. Nkx2.5 is thought to promote cardiomyocyte differentiation, and the balance of a progenitor state versus a differentiated state is maintained by Nkx2.5 competing with Isl1 and Meis factors (option C).^{14,15} In addition, *Pitx2c* is expressed in the left side of the SHF, as part of its general role in left-right patterning of lateral plate derivatives in the embryo (option B).¹⁶ While transcription factors can trigger gene expression, access to a locus occurs at the chromatin level. Recent work has highlighted the role of HDACs to deacetylate chromatin, leading to the repression of expression at a locus. Conversely, p300/CBP acetylate histones lead to gene activation (option D). Further, tissue-specific isoforms, such as the Mel1 isoform of PRC1, are important for dictating tissue-specific gene expression programs (option E).¹⁷
- 8-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 8*) Cardiac morphogenesis starts at 3.5 weeks. In the 12th week, outflow tract subdivision and complete interventricular and atrial septation lead to a heart bearing the gross morphological organization of a definitive adult heart (option A).⁸ The heart initially starts as a tube with an inner endocardium. Cardiac jelly is secreted by cardiomyocytes, and it prevents blood flow through the heart tube until the valves are competent (option B). Localized regions of proliferation lead to chamber ballooning. Tbx2 and 3 are important repressors of differentiation, but Tbx20 is required for chamber maturation (option C).^{1,18} Following looping, chamber formation results from localized proliferation and ballooning of the chambers (option D).^{19,20} The trabecular myocardium initially preserves cardiac output but is incorporated into the compact myocardium during compaction (option E).
- 8-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 8*) Cardiac septation occurs during the seventh week with the growth of a muscular ventricular septum between the right and left ventricles (option E). Later, a membranous septum grows between the muscular septum and the mesenchyme that contains the AV cushions. Atrial septation occurs first with a septum primum that grows between the atria, but that leaves a foramen primum between the septum primum and the AV cushions (option B). As the foramen primum is closed, a second foramen secundum develops in the septum primum (option A). A second septum secundum develops and occludes the foramen secundum. However, the septum secundum contains the foramen ovale, which allows for right-to-left blood flow but not the reverse. The foramen ovale closes due to fusion of the septum primum and secundum. Failure to fuse can lead to a persistent PFO (option C).²¹
- 8-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 8*) The aortic arch and pulmonary artery result from extensive remodeling of the embryonic aortic arch arteries. The six aortic arch artery pairs develop into five pairs of branchial arch arteries. The fifth aortic arch artery pair undergoes involution and does not contribute to a branchial arch artery pair (option B). The first two pharyngeal artery pairs and the right VI artery regress and do not produce any definitive contribution to the adult aorta (option D). The left VI artery forms the pulmonary trunk and pulmonary arteries (option C). The III pair of arteries forms the common carotid arteries, and the IV pair of arteries makes small contributions to the right subclavian artery and aortic arch. The pulmonary trunk remains attached to the aorta through the ductus arteriosus, which closes and involutes at birth (option E). Outflow tract septation results from the contribution of migrating neural crest and second heart field precursors (option A).²² Defects can lead to truncus arteriosus.
- 8-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 8*) The epicardium is the outer mesothelial layer of the heart that makes important contributions to the noncardiomyocyte cells of the heart. The epicardium is an epithelial sheet that covers the heart and can undergo EMT to become smooth muscle cells or fibroblasts (option A). The epicardium is heterogeneous, and some subsets may contribute to the endocardium and coronary endothelium (options B and E).²³⁻²⁵ The epicardium forms from the proepicardium, which derives from the coelomic epithelium (option D).²⁶ In the adult heart, the epicardium is activated following injury. The epicardium proliferates and invades the injured area (option C).^{27,28}

8-10. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 8*) Cardiomyocytes are originally added to the developing heart by the expansion and differentiation of progenitor cells. Over time, additional cardiomyocytes are added to the heart by symmetric division of cardiomyocytes. The capacity for cardiomyocyte proliferation wanes with time, but recent work has suggested a low grade of cardiomyocyte proliferation and renewal in the adult heart (option A).²⁹ The conduction system is a set of specialized cells that coordinate ordered chamber contraction. Cells of the conduction system, such as the Purkinje cells, have less contractility than the working myocardium. They have decreased numbers of mitochondria and disorganized sarcomeres (option E). The cellular origins of the conduction systems are diverse. For example, the SA node is derived from both first and second heart field progenitors (option B).^{30,31} The coronary endothelium starts to develop as cardiac muscle thickens. The coronary endothelium has diverse cellular origins, including the sinus venosus endothelium, the ventricular endocardium, and potentially a subset of epicardial cells (option D).^{23,32-36} Finally, coronary development is also important for the innervation pattern of the heart (option C).

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CHAPTER 9

Genetic Basis of Cardiovascular Disease

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

9-1. A 23-year-old woman presents with a long history of muscle weakness. Her past medical history is notable for “hypertrophic” cardiomyopathy (HCM), cryptogenic stroke, and optic neuritis. She was told that she had a dilated cardiomyopathy prior to developing a hypertrophic cardiomyopathy. Physical examination, in addition to findings of HCM, are remarkable for short stature and hearing loss. Labs are notable for an elevated CPK. Her family history includes multiple family members with cardiac problems. Her pedigree is shown in Figure 9-1. Her brother has a similar constellation of findings of similar severity. Her mother, her maternal grandmother, and her maternal uncle also have a similar set of findings but with milder severity. Based on the presentation and pedigree, what is the likely mode of inheritance?

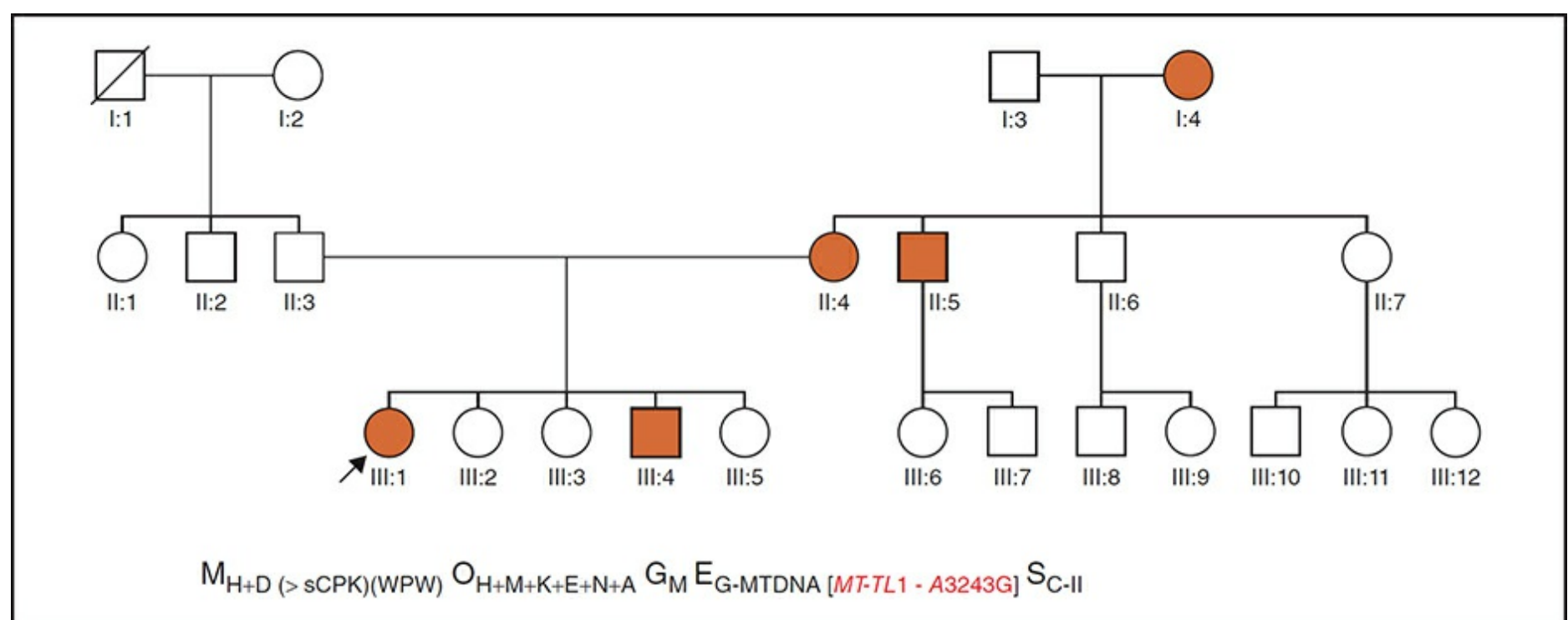


FIGURE 9-1 Pedigree for question 9-1.

- A. Autosomal recessive
 - B. Spontaneous somatic mutation
 - C. X-linked
 - D. Mitochondrial inheritance
 - E. Spontaneous chromosomal translocation
- 9-2.** Which of the following is *true* of heritable cardiomyopathies?
- A. About 1 in 500 people carry a gene associated with HCM
 - B. Patients with sarcomeric mutations can have either a hypertrophic, dilated, or restrictive cardiomyopathy
 - C. Most heritable cardiomyopathies are autosomal recessive
 - D. Heritable cardiomyopathies are rare
 - E. Patients with heritable cardiomyopathies only have mutations in sarcomeric genes
- 9-3.** A 38-year-old man is admitted with acute aortic dissection. Upon inquiry, he is noted to have a strong family history of aortic disease with dissection. Which of the following is *not true* about heritable thoracic aortic diseases?
- A. Genetic disorders with increased risk for thoracic aortic dissection are associated with mutations in genes related to extracellular matrix proteins and TGF- β signaling

- B. Patients with bicuspid aortic valves are at increased risk for aortic dilation
 - C. He most likely has an autosomal dominant genetic syndrome
 - D. A bifid uvula would suggest a diagnosis of Marfan syndrome
 - E. Translucent skin would suggest a diagnosis of Ehlers–Danlos syndrome
- 9-4. A 28-year-old woman is sent to you for evaluation of shortness of breath. Her examination reveals elevated neck veins, a right ventricular (RV) heave, and a loud P2. Echocardiography confirms the presence of pulmonary hypertension (PH). Family history is notable for multiple members with PH. Which of the following is *true* about heritable PH?
- A. Familial PH is classified as type 2 PH
 - B. The most common form of heritable PH is associated with a mutation in *BMPR2*
 - C. Less common mutations in PH include mutations in *FBN1*
 - D. The presence of multiple telangiectasias would suggest a diagnosis of Gaucher disease
 - E. Mutations in *BMPR2* are only associated with familial PH
- 9-5. Which of the following is *not true* of inherited atrial diseases?
- A. Mutations of *NPPA* are associated with an autosomal recessive atrial dilated cardiomyopathy
 - B. Mutations in *SCN5A* are associated with heritable sick sinus syndrome, LQT3, and Brugada syndrome
 - C. Mutations of *HCN4* are associated with heritable sick sinus syndrome
 - D. Mutations in the gene *Shugosin-like 1* are associated with chronic atrial and intestinal dysrhythmia (CAID)
 - E. Having a parent with atrial fibrillation has no effect on one's risk for developing atrial fibrillation
- 9-6. A 28-year-old man is admitted for syncope following exercise. He has no other prior medical history, and physical examination is normal. Family history is notable for a history of sudden cardiac death. ECG shows evidence of a long QT interval with broad-based T waves. This patient most likely has a mutation in which ion channel?
- A. *NPPA*
 - B. *SCN5A*
 - C. *KCNQ1*
 - D. *KCNH2*
 - E. *HCN4*
- 9-7. A 34-year-old man presents after resuscitation following cardiac arrest. He is otherwise healthy. ECG shows ST elevation in the anterior precordial leads. Which of the following is *not true* about Brugada syndrome?
- A. Brugada syndrome is more common in Southeast Asia
 - B. Brugada syndrome is associated with mutations in *RYR2*
 - C. The ECG manifestations of Brugada syndrome can be variable, but they are induced with drugs like ajmaline
 - D. Arrhythmia can be exacerbated by fevers
 - E. Arrhythmia can be exacerbated by interactions with certain drugs
- 9-8. A 35-year-old man presents with atrial arrhythmias. He has a past medical history of thyroid tumors. The physical exam is notable for pigmented skin lesions. Echocardiogram shows the presence of an atrial myxoma. Which of the following is *true* of his syndrome?
- A. His syndrome is associated with mutations in the *PTCH1* gene
 - B. His syndrome is associated with an increased incidence of pancreatic tumors
 - C. Histologically, the myocytes are round and vacuolated
 - D. His myxoma will likely respond to rapamycin
 - E. He is at increased risk for medulloblastoma
- 9-9. A 21-year-old female presents to you for evaluation of chest pain. She has had recurring bouts of chest pain since she was 8 years old. Her chest pain is worse when lying supine and improves when sitting upright. Her chest pain is also made worse with deep inspiration. In addition to chest pain, she has abdominal pain and fevers during these episodes. The episodes are self-limited and have no specific trigger. Family history of a similar disorder is not known. Which of the following is *true* of familial Mediterranean fever (FMF)?
- A. FMF is autosomal dominant
 - B. FMF is the result of a mutation in the *G6PD* gene
 - C. The chest pain and abdominal pain are part of a pan-serositis
 - D. The disease is most common in Western European populations
 - E. Heterozygous patients are not at risk for the periodic fever syndrome
- 9-10. Which of the following is *true* about the genetic basis of coronary heart disease (CHD)?
- A. Most of the genetic variants that contribute to CHD are known
 - B. Twin studies show a decreased risk of CHD if the other twin died of premature CHD
 - C. The 9p21-3 allele is associated with a high risk for CHD

- D. Most heritable CHD is due to monogenic disorder
- E. Single nucleotide polymorphisms (SNPs) that contribute to CHD are uncommon

ANSWERS

- 9-1. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 9*) The patient has a syndrome of mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS). MELAS patients can have a dilated cardiomyopathy that transitions to a HCM.¹ MELAS is a mitochondrial myopathy and often is the result of a mutation in transfer RNA (option D). The pedigree shows the phenotype in every generation. Spontaneous mutations would not be in each generation (options B and E). Autosomal recessive mutations skip every generation (option A). Similarly, X-linked mutations tend to involve males because males have a single X chromosome (option C). Autosomal dominant mutations result in affected family members in each generation, but this is not a choice. Mitochondrial DNA is maternally derived, so the disease can only be passed by females. The penetrance of the disease is related to the amount of abnormal mitochondrial DNA that is inherited.
- 9-2. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 9*) Hypertrophic cardiomyopathy is the most common heritable cardiomyopathy. One in 500 young adults are affected, and 1 in 200 people carry a mutation that is associated with HCM (option A).² While patients with HCM primarily have mutations of sarcomeric proteins, sarcomeric mutations can result in either a hypertrophic, dilated, or restrictive cardiomyopathy (option B).³ While the full complement of mutations leading to heritable cardiomyopathies remains unknown, up to 80% of heritable cardiomyopathies are autosomal dominant (options C and E).⁴ Furthermore, heritable cardiomyopathies are common, with more than 50% of patients with dilated cardiomyopathy having evidence for an underlying genetic cause (option D).⁴
- 9-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 9*) Heritable thoracic aortic aneurysm and dissection (TAAD) includes more than 40 genetically different disorders. The genetic basis for these disorders is diverse, and many involve mutations in genes related to extracellular matrix proteins and TGF- β signaling (option A). For example, Marfan syndrome is associated with mutations in the extracellular matrix protein *FBN1*, and mutations of *TGFBR1* and *TGBFR2* cause Loeys–Dietz syndrome type 1 (LDS1) and Loeys–Dietz syndrome type 2 (LDS2), respectively.⁵ In 25% of cases, patients with bicuspid aortic valves have dilation of the ascending aorta (option B).⁶ Most heritable thoracic aortic aneurysm disorders (TAAD) are autosomal dominant (option C). Different TAAD syndromes are associated with other clinical features. Patients with Marfan syndrome have typical skeletal traits. LDS1 patients have craniofacial traits, including a bifid uvula and craniosynostosis (option D). Patients with Ehlers–Danlos type IV (EDSIV) have a typical skin and face morphology. Facial features include a thin nose, thin lips, prominent eyes, hollow cheeks, a small chin, and lobeless ears. The skin is very thin and nearly translucent, allowing for visualization of the underlying blood vessels (option E).
- 9-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 9*) The WHO classifies PH in five groups.⁷ Group 1 includes idiopathic PH, heritable PH, drug-induced PH, CHD with PH, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis. Group 2 includes PH related to left heart disease (option A). Group 3 includes PH secondary to lung disease. Group 4 includes chronic thromboembolic PAH. Group 5 PH includes miscellaneous disorders that can affect the pulmonary vasculature with unclear or multifactorial mechanisms. Up to 80% of patients with familial autosomal dominant PH have mutations in *BMPR2* (option B).⁸ Similarly, up to 20% of sporadic PH is associated with acquired mutations of *BMPR2* (option E). Mutations in *FBN1* are associated with Marfan syndrome (option C). While Gaucher disease can be associated with PH, telangiectasias are associated with Osler–Weber–Rendu syndrome (option D).
- 9-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 9*) Atrial dilated cardiomyopathy (ADCM) is a rare autosomal recessive disease that manifests as biatrial dilation with progression to electrical standstill of the atria. ADCM is associated with mutation of the *NPPA* gene (option A).⁹ *SCN5A* encodes a key sodium channel within the heart, and different mutations of *SCN5A* are associated with various arrhythmias, including sick sinus syndrome, LQT3, and Brugada syndrome (option B).^{10–14} Mutations of *HCN4* are also associated with a heritable sick sinus syndrome (option C). CAID is associated with mutations in the *Shugosin-like 1* gene and manifests with atrial dysrhythmias and chronic intestinal pseudo-obstruction (option D). The genetic basis for familial atrial fibrillation is not as clear for other arrhythmias, but having an affected parent increases a person's risk for developing atrial fibrillation by 85% (option E).¹⁵
- 9-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 9*) This patient has LQT1. LQT1 manifests with exercise-induced arrhythmias. ECG shows broad T waves with a prolonged QT interval. LQT1 involves mutations in *KCNQ1*, and it can be treated with beta blockade (option C). Mutations in *NPPA* are associated with heritable atrial dilated cardiomyopathy (option A). Mutations in *SCN5A* are associated with LQT3, SSS, and Brugada syndrome (option B). Mutations in *KCNH2* are associated with LQT2 (option D). Mutations in *HCN4* are associated with heritable sick sinus syndrome (option E).

- 9-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 9*) Brugada syndrome is a genetic syndrome that is associated with increased risk for sudden cardiac death. Brugada syndrome is heritable, most commonly involving mutations of *SCN5A*, and it tends to occur most commonly in patients from Southeast Asia (options A and B).¹⁶ The ECG typically has ST elevations in the anterior precordial leads. However, these findings are not always readily apparent. Drugs like ajmaline can elicit a more classical pattern in such patients (option C). Arrhythmias can occur with sensitizing factors like fever or drugs (options D and E).
- 9-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 9*) This patient has Carney syndrome. Type I Carney complex is associated with mutations in the *PRKAR1A* gene (option A). As many as 2.5% of patients with Carney syndrome have pancreatic tumors (option B).¹⁷ Purkinje cell hamartomas, not atrial myxomas, are associated with round and vacuolated myocytes (option C). mTOR inhibitors are used to treat rhabdomyomas associated with tuberous sclerosis (option D).¹⁸ Medulloblastoma is associated with cardiac fibromas and Gorlin
- 9-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 9*) Familial Mediterranean fever is a rare autosomal recessive disorder, most common in patients of Eastern European ancestry (options A and D).¹⁹ FMF is most commonly caused by a mutation in the *MEFV* gene that encodes pyrin, a component of the cellular inflammasome (option B). Patients typically present with abdominal pain and chest pain indicative of serositis (option C). Heterozygous patients can also manifest the disease during stresses, or they can alternatively present with other inflammatory syndromes
- 9-10. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 9*) Coronary heart disease is a prototypical complex genetic disease (option D). The genetic basis for CHD has been supported by twin studies showing an increased risk for CHD in the second twin when the first twin dies of CHD (option B).²³ Large-scale, genome-wide association studies have identified multiple common SNPs associated with CHD (option E). Together, these SNPs account for about 10% of the heritable basis for CHD (option A).²⁴ Each SNP generally has a small effect. However, the 9p21-3 allele, in particular, is considered a high risk for CHD (option C).^{25,26}

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CHAPTER 10

Stem Cells and the Cardiovascular System

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

10-1. Which of the following is *not true* about mechanisms of cell therapy?

- A. Transdifferentiation is when a differentiated cell type commits to becoming a new cell type
- B. Angiogenesis is the formation of new blood vessels
- C. Bone marrow cell therapy is likely to promote ventricular recovery by transdifferentiation into cardiomyocytes
- D. Dedifferentiation likely confers a protective effect for injured cardiomyocytes
- E. Transplanted bone marrow cells are transiently retained in the heart following cardiac injury

10-2. Which of the following is *true* of stem cell delivery approaches to the heart?

- A. Intracoronary injection of stem cells results in better engraftment of cells than transendocardial injection
- B. Transendocardial injection does not require adjunctive imaging modalities to target injured myocardium
- C. Intravenous administration of stem cells is a promising approach because stem cell populations evaluated thus far are efficient in their homing to injured myocardium
- D. Transepical injection of stem cells requires adjunctive imaging modalities to target injured myocardium
- E. Activation of resident stem cells has been evaluated in human studies after acute myocardial infarction (MI)

10-3. Which of the following limits the clinical application of skeletal myoblasts to improve cardiac function following injury?

- A. Skeletal myoblasts do not share contractile properties with cardiomyocytes
- B. Skeletal myoblasts are difficult to isolate
- C. Skeletal myoblasts are difficult to expand
- D. Skeletal myoblasts do not readily adapt to a hypoxic environment
- E. Skeletal myoblasts do not electrically couple to the myocardium and may increase the risk for arrhythmia

10-4. A 54-year-old man presents to your office asking for stem cell therapy. He recently had a large anterior infarct with residual left ventricular (LV) dysfunction. He has read about bone marrow mononuclear cell (BMMNC) therapy and would like some guidance. Which of the following can you tell him?

- A. The cells responsible for improving LV function in preclinical models are hematopoietic progenitor cells
- B. Early clinical studies after acute MI demonstrate an unequivocal increase in LV function after treatment with BMMNCs
- C. BMMNCs can be administered relatively safely, but their efficacy is not proven following acute MI or for chronic heart failure
- D. Treatment with BMMNCs improves functional status but not ventricular function
- E. None of the above

10-5. The patient from question 10-4 returns to your clinic and is now asking about treatment with mesenchymal stem cells (MSCs). Which of the following can you tell him?

- A. Unlike BMMNCs, allogeneic MSCs require immunosuppression
- B. MSCs are more effective than BMMNCs for improving ventricular function following acute MI
- C. MSCs can differentiate into cardiac progenitors in vivo
- D. MSCs from different sources, such as the bone marrow or Wharton's jelly, are equivalent
- E. Preliminary data on MSCs for the treatment of cardiovascular disease are promising, but additional studies are needed before routine use can be recommended

10-6. Which of the following is *not true* about angiogenic progenitor cells (APCs)?

- A. APCs give rise primarily to endothelial cells

- B. Intracoronary injection of CD34⁺ APCs can reduce angina, but they are associated with small elevations of cardiac biomarkers
- C. APCs for the treatment of heart failure have had mixed results
- D. Patients with nonischemic heart failure have normally functioning APCs
- E. Early studies do not suggest a benefit of APCs for peripheral arterial disease (PAD)

10-7. Which of the following is *true* of adipose stem cells?

- A. MSCs derived from adipose tissue are attractive for cell therapy because they are more easily obtained than bone marrow MSCs
- B. Adipose-derived MSCs can be differentiated to cardiomyocytes in vivo
- C. Adipose tissue can be transdifferentiated to endothelium in vivo
- D. The number of adipose-derived MSCs is related to glucose sensitivity
- E. Adipose-derived MSCs are limited by adverse events in early clinical trials

10-8. A 65-year-old woman presents to your clinic for advice about stem cell therapy. She brings in a brochure for the use of cardiac stem cells and wants to know your thoughts on stem cell therapy for the heart. She has a nonischemic cardiomyopathy with reduced LV function (LVEF 25%) and class III heart failure symptoms. Her ECG reveals a left bundle branch block with a QRS duration of 150 ms. She has been taking guideline-directed medical therapy for her heart failure and has an implantable defibrillator. She is very intent on going to a stem cell clinic. Which of the following can you use to advise her?

- A. Cardiac stem cells are known to promote heart regeneration in preclinical models
- B. Current approaches to isolate resident cardiac stem cells include harvest from peripheral blood
- C. A resident stem cell population in the heart has been clearly identified, but work regarding clinical efficacy is still preliminary
- D. She is more likely to benefit from an upgrade of her ICD to a biventricular pacing system
- E. Cardiac progenitor cells are a promising approach to treat heart failure and should be sought out to the best of one's ability

10-9. Which of the following is *not* a limitation to using embryonic stem (ES) cells for cardiac cell therapy?

- A. Obtaining ES cells for cell therapy is limited by ethical controversies
- B. ES cells would be used as an autologous cell source, requiring immunosuppression after transplantation
- C. ES cells are potentially tumorigenic
- D. Protocols for robustly differentiating ES cells into cardiomyocytes are lacking
- E. Evidence is lacking for the clinical efficacy of ES cells for heart regeneration

10-10. Which of the following is *not true* regarding induced pluripotent stem cells (iPSCs)?

- A. iPSCs can be used to generate autologous cardiomyocytes for cell therapy
- B. The generation of iPSCs from somatic cells has the potential for tumorigenesis
- C. iPSCs can be used to model genetic diseases
- D. Like ES cells, the generation of iPSCs remains controversial
- E. iPSCs can provide a human model system for fundamental mechanistic work

ANSWERS

10-1. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 10*) Multiple groups have tested the efficacy of bone marrow cell therapy after MI. Bone marrow cells in preclinical models rarely transdifferentiate into cardiomyocytes (options A and C), are transiently retained in the heart (option E), and most likely exert their beneficial effects on cardiac function through a paracrine mechanism that stimulates new blood vessels through angiogenesis (option B).¹⁻⁴ Lastly, a novel concept in cardiac repair is modulation of dedifferentiation. Dedifferentiation is the process by which cardiomyocytes take on a gene and protein expression profile that is more similar to fetal. This phenotype occurs more often in acute and chronic injury of the heart and seems to confer a potential survival advantage of these cardiomyocytes (option D).

10-2. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 10*) While additional work is needed for cell therapy to be considered a treatment modality, the science of stem cell delivery has rapidly developed. Current approaches include intravenous delivery, but this is limited by poor retention of stem cells in the myocardium (option C). Intracoronary injection of stem cells can be done during percutaneous coronary intervention, but stem cell retention is not as good as with transendocardial injection (option A).^{4,5} Transendocardial injection can also be done in the catheterization laboratory, but it requires advanced imaging to identify target areas for injection (option B). Transepical injection may be of similar value, but it requires direct visualization of the heart (option D).⁶ An alternative to intracardiac

injection is activation of resident stem cells, but this approach remains in preclinical investigation (option E).

- 10-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 10*) Skeletal myoblasts are skeletal muscle precursor cells derived from skeletal muscle satellite cells. Interest in this population was supported by similarity to adult cardiomyocytes, the potential for autologous utilization, ease of expansion in vitro, and resistance to hypoxic environment (options A through D). However, the MAGIC clinic trial and other pilot studies showed an increased risk for arrhythmia.⁷ Functionally, skeletal muscle fails to couple with endogenous cardiac muscle (option E).⁸
- 10-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 10*) Several preclinical studies showed an improvement in ventricular function after MI with infusion of BMMNCs.^{9,10} However, these findings have since proven controversial. Key questions remain as to the mechanism of action and the cell type responsible for the reverse remodeling that has been observed (option A). Nonetheless, human trials have been taking place for nearly two decades. These have been mostly small trials of variable design, and meta-analyses for treatment following acute MI or for ischemic cardiomyopathy have shown mixed results for improving ventricular function or functional status (options B and D).¹¹ While the science of BMMNCs is still developing, methods of delivery have evolved, and catheter-based delivery of BMMNCs has proven to be relatively safe (option C).
- 10-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 10*) MSCs are a promising source for cell therapy. MSCs arise from diverse sources and can be differentiated into multiple cell types, including cardiomyocytes, in vitro (option C).^{12,13} Unlike BMMNCs, MSCs are thought to be immune privileged, raising the possibility for allogeneic transplantation without immunosuppression (option A). The POSEIDON trial evaluated MSCs in patients with ischemic cardiomyopathy. Interestingly, the autologous MSC group showed improved 6-minute walk distances and Minnesota Living with Heart Failure Questionnaire scores, whereas the allogeneic MSCs group showed a reduction in LV end-diastolic dimension. Both groups showed a reduction in infarct size (option B).¹⁴ MSCs from different sources may have differing efficacies, but MSCs from different sources have yet to be tested for comparative efficacy (option D). Finally, like BMMNCs, clinical studies for MSCs are small, and additional studies are needed before MSCs can be recommended therapeutically (option B).
- 10-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 10*) APCs are a population of progenitor cells that mainly give rise to endothelial cells (option A).¹⁵ Patients with nonischemic heart failure have functionally impaired APCs (option D). Vrtovc et al. conducted one of the largest randomized trials, with 110 nonischemic cardiomyopathy patients randomized to receive either CD34⁺ intracoronary infusion or standard therapy. At 12 and 60 months, the CD34⁺ treatment group showed a significant improvement in LVEF and 6-minute walk distance.¹⁶ However, injection of CD133⁺ cells led to improved myocardial perfusion but resulted in a lower LVEF, and no difference in functional capacity.¹⁷ This study contradicted findings from prior nonrandomized studies that investigated CD133⁺ cells (option C).¹⁸ APCs are promising for the treatment of chronic angina, but intracoronary infusion has been associated with small elevations of cardiac biomarkers (option B).^{19,20} Patients with nonischemic heart failure have abnormally functioning APCs (option D).²¹ Multiple studies have examined the role of APCs in the treatment of PAD, with most showing an excellent safety profile with marginal to no benefit (option E).^{19,22-24}
- 10-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 10*) Adipose tissue harbors a heterogeneous set of progenitor cells, mostly MSCs. These MSCs are attractive because they can be obtained from liposuction, which is easier than bone marrow biopsy (option A). The study of adipose-derived stem cells is still early. MSC cell fates in vivo are still being explored, and conditions for generating MSCs are still being optimized (options B through D). Initial clinical work suggests safety, but additional studies are needed to evaluate efficacy (option E).^{25,26}
- 10-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 10*) Despite nearly two decades of preclinical research, cardiac progenitor cells remain very controversial. Beyond issues of identity, whether the postnatal heart harbors a population of resident progenitor cells has been hotly debated (options A and C).^{27,28} Several groups have pushed forward with putative cardiac stem cells. These groups rely on harvest of stem cells from the heart for expansion and then retransplantation (option B).^{29,30} Early results are promising, but definitive results for clinical efficacy remain. This patient is the ideal candidate for cardiac resynchronization therapy, and upgrading her device to a biventricular pacing system should be strongly recommended before pursuing less proven approaches (options D and E).
- 10-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 10*) The isolation and expansion of human ES cells was a formidable scientific achievement. Many groups have used this model to understand mechanisms of development and to develop protocols for robustly differentiating ES cells into specific cell types, such as cardiomyocytes. Current protocols allow for differentiation, expansion, and isolation of cardiomyocytes with greater than 90% purity (option D).^{31,32} However, widespread use of ES cells to make new cardiomyocytes remains limited by controversy in obtaining new lines of ES cells, concerns for the tumorigenic potential of transplanted ES cells, and the possible need for immunosuppression after the transplantation of ES cells (options A, B, and C).³³ Initial clinical trials testing ES cells in patients with ischemic cardiomyopathy are underway (option E).
- 10-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 10*) The ability to transform somatic cells to pluripotency was

a major scientific achievement. The delivery of a cocktail of factors can generate ES-cell–like cells from somatic cellular sources, including fibroblasts and urinary epithelial cells. Thus, iPSCs can be developed to represent individual patients without the ethical concerns surrounding ES cells (option D). As with ES cells, however, concerns remain about the tumorigenic potential of transplanted iPSC cells (option B). Unlike ES cells, because a patient’s own cells can be reprogrammed to cardiomyocytes, the possibility exists for autologous cell therapy not requiring immunosuppression (option A). Over the past decade, iPSCs have been used to model genetic cardiovascular diseases and to create platforms for assessing drug safety. Further, iPSC-derived models of disease are being used to better understand the mechanisms that underlie many genetic disorders (option E). Disease modeling is primarily limited to heritable, cell-autonomous disorders (option C).

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SECTION 3

Evaluation of the Patient

CHAPTER 11

The History, Physical Examination, and Cardiac Auscultation

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 11-1.** All of the following findings would suggest a diagnosis of hypertrophic cardiomyopathy *except*:
- A. Paradoxically split S2
 - B. Bifid pulse
 - C. “Triple ripple” apical impulse
 - D. S4
 - E. Fixed split S2
- 11-2.** A 35-year-old man with a history of intravenous drug abuse and known bicuspid aortic valve presents with increasing shortness of breath, fevers, and lethargy. All of the following physical examination findings would suggest a diagnosis of aortic insufficiency complicating infective endocarditis *except*:
- A. Bisferiens pulse
 - B. A high-pitched, “cooing,” diastolic murmur
 - C. A middiastolic rumble
 - D. Diastolic murmur best heard over the second right intercostal space
 - E. Arterial pulse that is increased in amplitude
- 11-3.** A 59-year-old man presents with several episodes of substernal chest pressure of 15 minutes’ duration, which was brought on by an argument with his neighbor. His pain is relieved by nitroglycerine. According to the Forrester and Diamond chest pain classification, this patient’s angina would be described as:
- A. Noncardiac chest pain
 - B. Atypical angina
 - C. Typical angina
 - D. Dyspnea
 - E. Walk-through angina
- 11-4.** A 76-year-old woman with severe aortic stenosis presents with dyspnea and worsening functional class in the setting of new-onset atrial fibrillation. Which of the following auscultatory findings would *not* be expected?
- A. A late-peaking crescendo-decrescendo systolic murmur
 - B. A soft S2
 - C. An apical systolic murmur
 - D. Delayed and weak carotid upstroke
 - E. An S4
- 11-5.** The simultaneous left ventricular and aortic pressure tracings ([Figure 11-1](#)) are obtained from two different patients undergoing cardiac catheterization for dyspnea. Which of the following diagnoses are suggested in [Figure 11-1\(a\)](#) and [Figure 11-1\(b\)](#), respectively?

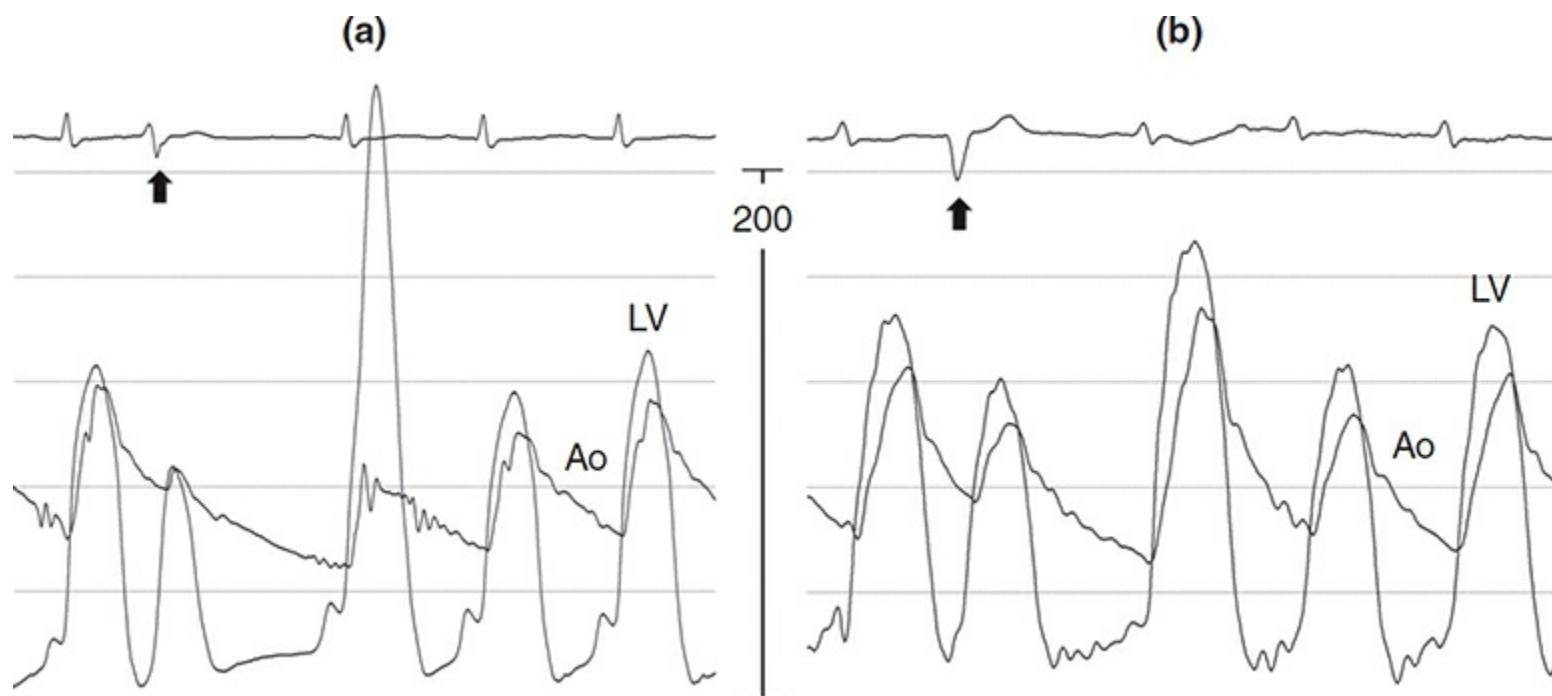


FIGURE 11-1 Simultaneous aortic and left ventricular pressure tracings taken from two patients (*a* and *b*).

- A. Aortic stenosis and hypertrophic obstructive cardiomyopathy (HOCM), respectively
 - B. Hypertrophic obstructive cardiomyopathy and aortic stenosis, respectively
 - C. Mitral stenosis and aortic stenosis, respectively
 - D. Mitral regurgitation and mitral stenosis, respectively
 - E. Hypertrophic obstructive cardiomyopathy and mitral stenosis, respectively
- 11-6.** A 25-year-old woman is referred for a murmur. Transthoracic echocardiography demonstrates mitral valve prolapse. Which of the following is *true* about the click accompanying mitral valve prolapse?
- A. This usually occurs in early systole
 - B. Upon standing, the click will occur earlier in systole
 - C. It decreases in intensity with inspiration and moves closer to S1
 - D. This is a lough, high-pitched sound
 - E. Upon Valsalva maneuver, the click will occur later in systole
- 11-7.** A 34-year-old man presents with a family history of bicuspid aortic valve disease. On auscultation, a loud murmur is heard at the upper sternal border. No thrill is palpable. How should this murmur be graded?
- A. Grade I
 - B. Grade II
 - C. Grade III
 - D. Grade IV
 - E. Grade V or Grade VI
- 11-8.** A 45-year-old woman is referred for a murmur. Which finding on physical examination would be suggestive of a diagnosis of HOCM?
- A. A decrease in the intensity of the systolic murmur upon standing
 - B. A midsystolic click
 - C. A decrease in the systolic ejection murmur with inspiration
 - D. A palpable P2
 - E. An apical holosystolic murmur
- 11-9.** An 18-year-old asymptomatic man is referred for a murmur. The murmur is continuous, present in systole and diastole, and is characterized by a “to-and-fro” sound. The differential diagnosis should include all of the following *except*:
- A. Ruptured sinus of Valsalva aneurysm
 - B. Arteriovenous fistula
 - C. Patent ductus arteriosus
 - D. Severe coarctation of the aorta
 - E. Mixed aortic valve disease (aortic stenosis and aortic regurgitation)
- 11-10.** A 67-year-old woman presents with three days’ duration stuttering chest pressure radiating to her jaw and arm. ECG demonstrates inferior ST-segment elevations. In the emergency room, she suddenly develops worsening shortness of breath. Which of the following physical exam findings could help distinguish acute mitral regurgitation from acute ventricular septal rupture?
- A. Assessment of dyspnea in supine and upright positions
 - B. Soft systolic murmur

- C. Cool extremities
- D. Increased jugular venous pressure
- E. S3

ANSWERS

- 11-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 11*) Fixed splitting of S2 is classically found in ostium secundum atrial septal defect, where wide splitting of S2 is present at baseline with minimal or no change in the A2-P2 interval during inspiration. Conversely, paradoxical splitting of the S2 is more common in obstructive hypertrophic cardiomyopathy, suggesting severe dynamic left ventricular outflow obstruction. Hypertrophic cardiomyopathy with obstruction is a cause of a bifid pulse, caused by the occurrence of obstruction starting in midsystole. This is seen as a spike-and-dome pattern on aortic pressure tracing. Patients with HOCM might also have a classic apical impulse—the so-called triple ripple—corresponding to the presence of palpable systolic impulse in early and midsystole, separated by withdrawal of the apical impulse related to dynamic outflow obstruction; a palpable atrial contraction corresponds to the third impulse. An S4 is often heard in patients with abnormalities of ventricular relaxation, such as hypertrophic cardiomyopathy.
- 11-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 11*) Aortic regurgitation murmurs heard over the second right intercostal space result from annular dilatation, whereas murmurs heard over the third left intercostal space result from a valvular process. When mixed aortic valve disease is present and the aortic regurgitation is the predominant lesion, an arterial contour with increased amplitude and two palpable systolic peaks can be present—the bisferiens pulse (option A is incorrect). The murmur of aortic regurgitation is a high-pitched “cooing” sound resulting from the high pressure difference between the aorta and left ventricular pressures during diastole (option B is incorrect). A middiastolic rumble, the Austin-Flint murmur, may be heard in aortic regurgitation when an eccentric jet hits the anterior leaflet of the mitral valve, causing it to reverberate and generating the apical rumble (option C is incorrect). In aortic regurgitation, the combination of increased stroke volume and the regurgitation itself gives rise to an arterial pulse that is increased in amplitude (“bounding”), which also collapses very quickly—the so-called water hammer pulse (option E is incorrect).
- 11-3. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 11*) Forrester and Diamond categorized chest pain into typical angina (all three criteria were present), atypical angina (two criteria), and noncardiac chest pain (only one criterion). They based this classification on whether the pain (1) was substernal and pressure-like, (2) was precipitated by exertion or emotional stress, and (3) was relieved by rest or nitroglycerin and lasted less than 30 minutes. In certain patient populations (eg, elderly men), this approach yielded such a high pretest probability of coronary artery disease that stress testing was unnecessary for the diagnosis of coronary atherosclerosis. This continues to be of value in clinical practice, particularly for male patients. It is commonly said that women often present with atypical symptoms, and the diagnosis of myocardial ischemia may be missed using these classic criteria. However, data suggest that anginal symptoms might be similar in men and women and that the idea that women often present with atypical symptoms might be misleading.¹ Rarely, patients will report that angina improves with continued exercise (walk-through angina).
- 11-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 11*) In the early phases of diastolic dysfunction, abnormal (prolonged) ventricular relaxation impairs early diastolic ventricular filling, decreasing the amount of filling in early diastole with a compensatory enhanced atrial contribution of diastolic filling.² An audible left heart fourth heart sound (S4) represents this prominent, forceful left atrial contraction into a noncompliant left ventricle. Therefore, although often present in patients with aortic stenosis and sinus rhythm, it is *never* present in atrial fibrillation (due to the loss of the *a* wave). When present, a left-sided S4 is a low-pitched sound, typically only heard at the apex with the bell and easily missed if auscultation in the left lateral decubitus position is not performed. Among the other findings, a late-peaking crescendo-decrescendo systolic murmur, a soft S2, and delayed and weak carotid upstroke (pulsus tardus and parvus) are all signs of severe aortic stenosis (options A, B, and D are incorrect). The murmur of aortic stenosis can radiate and, in fact, increase in intensity toward the apex—the Gallavardin phenomenon (option C is incorrect).³
- 11-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 11*) In patients with systolic murmur, attention should be paid to the change in intensity of the murmur on the postectopic beats. There is an increase in ventricular contractility and a decrease in afterload on the postectopic beat; thus, there will be an increase in the intensity of the murmur with both fixed (aortic stenosis) and dynamic (hypertrophic cardiomyopathy) left ventricular outflow tract obstruction. This response is much more striking in the setting of obstructive hypertrophic cardiomyopathy because there will also be an increase in the degree of obstruction ([Figure 11-1](#)). Alternatively, in patients with mitral regurgitation, there will be no change in the intensity of the murmur on the postectopic beat due to the decrease in afterload. Aortic and left ventricular pressure tracings illustrate the postectopic beat (arrow) response in dynamic outflow tract obstruction (left) versus fixed aortic stenosis (right). Although systolic gradients increase in both diseases, the response is much more exuberant in hypertrophic cardiomyopathy (the Brockenbrough-Braunwald-Morrow phenomenon).
- 11-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 11*) Systolic clicks can arise from valvular and nonvalvular

structures (eg, the great arteries). The two most common (and more relevant) clicks are the ones heard in bicuspid aortic valve and mitral valve prolapse. Although the former is typically described as an ejection click and the latter a nonejection click, a description based on timing is more appropriate. The systolic click associated with mitral valve prolapse usually occurs in mid-to-late systole (option A is incorrect), when there is full excursion of the prolapsed mitral leaflet(s) into the left atrium. The click can be single or multiple (salvo of clicks). The timing of the click of mitral valve prolapse occurring later in systole helps to differentiate it from clicks arising from semilunar valves. With increased preload (squatting, supine) the click occurs later in systole, whereas decreased preload (Valsalva maneuver, standing) has the opposite effect (Figure 11-2; option E is incorrect).

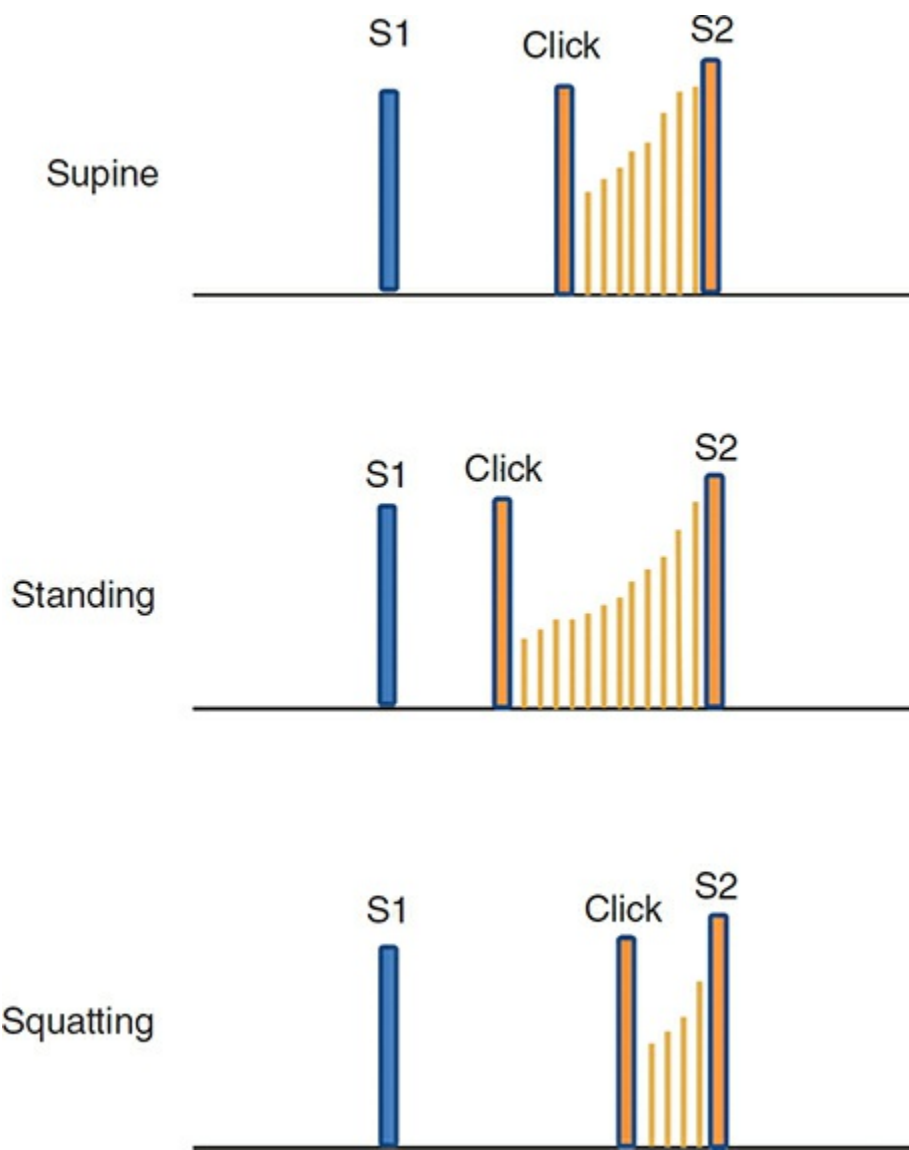


FIGURE 11-2 Positional changes in the systolic click and murmur of mitral valve prolapse. S1, first heart sound; S2, second heart sound.

Conversely, the click of a bicuspid aortic valve (and sometimes of other congenitally abnormal aortic valves such as unicuspid valves) is secondary to the doming of the valve cusps in early systole as the aortic valve opens. The sound is high-pitched (higher than S1) and sometimes quite loud; it should not be confused with a loud split S1 (two components of the same pitch and intensity) or an S4 (low-pitched sound that vanishes if the bell is firmly pressed against the skin) (option D is incorrect). Doming of the cusps is also seen in valvular pulmonary stenosis, and an early systolic click is also typical. As in bicuspid aortic valve, the click of pulmonary stenosis introduces the systolic murmur. However, the click noted in pulmonary stenosis has a unique and important characteristic: it decreases in intensity with inspiration and moves closer to S1 (option C is incorrect). This is the only right-sided auscultatory finding that diminishes with inspiration. Early systolic clicks can also arise from dilated great vessels (aorta or pulmonary artery).

11-7. The answer is C. (*Hurst’s The Heart, 14th Edition, Chap. 11*) Systolic murmurs are graded I to VI, as in the following table:

Grade I	Faint murmur; heard only after a few seconds of auscultation
Grade II	Moderately loud murmur heard immediately
Grade III	Loud murmur; not associated with a thrill
Grade IV	Loud murmur associated with a thrill
Grade V	Very loud; can be heard if only the edge of the stethoscope is in contact with the skin
Grade VI	Loudest possible; can be heard with the stethoscope just removed from the chest and not touching the skin

11-8. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 11*) The simultaneous left ventricular and aortic hemodynamic pressure tracings from a patient with HOCM shown in Figure 11-3 demonstrate characteristic respirophasic hemodynamic changes. Inspiration leads to increased left ventricular afterload; as a result, the systolic gradient between the left ventricle and the aorta decreases with inspiration. At the bedside, this is manifested by a decrease in the systolic ejection murmur noted with inspiration. The presence of this finding suggests dynamic instead of fixed outflow tract obstruction as the source of the murmur. Standing decreases preload and worsens obstruction in HOCM, which will make the murmur louder (option A is incorrect). A midsystolic click is not characteristic of HOCM (option B is incorrect); the approach to a click is reviewed in question 11-6. A palpable P2 can be observed in patients with advanced pulmonary hypertension; although secondary pulmonary hypertension (Group 2) can result from HOCM, this finding is not specific to HOCM (option D is incorrect). An apical holosystolic murmur suggests mitral regurgitation, and it is not specific to HOCM (option E is incorrect).

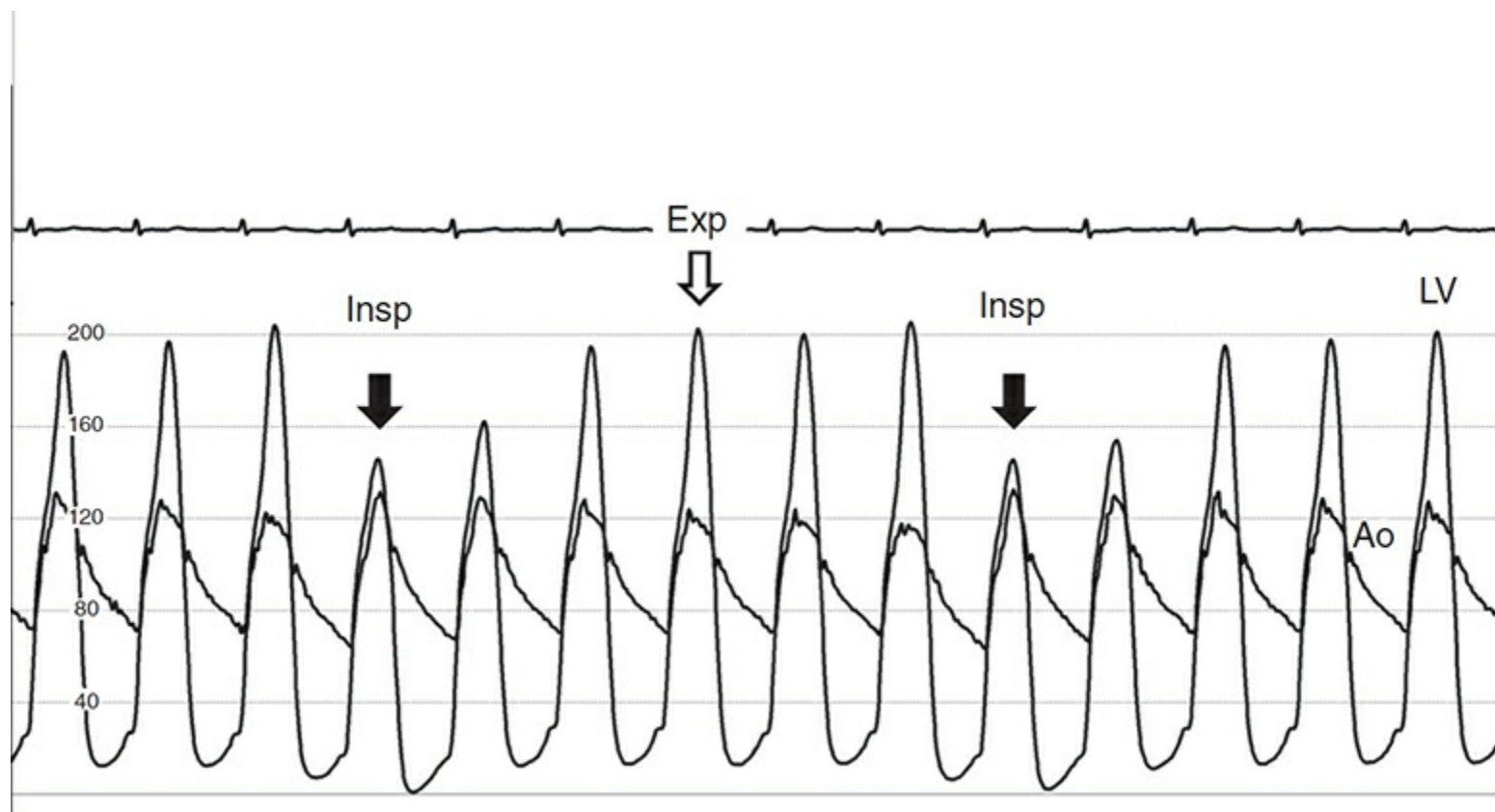


FIGURE 11-3 Simultaneous left ventricular and aortic hemodynamic pressure tracings from a patient with hypertrophic obstructive cardiomyopathy demonstrate characteristic respirophasic hemodynamic changes.

11-9. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 11*) The continuous murmur is characterized by a to-and-fro sound with no interruption between systole and diastole. The pitch should be similar, but the intensity can vary throughout the cardiac cycle. By definition, the continuous murmur envelops the heart sounds. This is distinctly different from a systolic and diastolic murmur, as noted in mixed aortic valve disease. In that case, one will hear a harsh, diamond-shaped systolic murmur, a second heart sound (which might be single), and a diastolic murmur. These murmurs will have two distinctly different pitches.

The most common continuous murmur seen in current practice is secondary to iatrogenic arteriovenous fistulas (for hemodialysis), which is generally appreciated in the region of the clavicle on the respective side (option B is incorrect). Other causes of continuous murmurs are rare and include patent ductus arteriosus (best heard over the left infraclavicular area), ruptured sinus of Valsalva aneurysm, coronary fistula, intrathoracic arteriovenous fistulae, severe coarctation of the aorta, and a surgically created shunt (eg, Blalock-Taussig, Potts, Waterston) (options A, C, and D are incorrect). The venous hum is a continuous murmur heard on auscultation of the neck. It results from a high flow in the internal jugular vein, which most likely causes a vibration of the venous wall. It is most commonly heard in young, otherwise healthy individuals and is not associated with pathology. The venous hum will disappear with the supine position or with compression of the vein itself.

11-10. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 11*) In acute severe mitral regurgitation secondary to papillary muscle rupture or mitral valve dehiscence, the left atrium is not accustomed to the severe volume overload. A very large v wave is generated because of lack of atrial compliance, and left ventricular and left atrial pressures essentially equalize in systole. The auscultatory result is a very short, early systolic murmur or even absence of a murmur. Accordingly, color-flow and continuous-wave Doppler findings are also often very brief, making the diagnosis of acute mitral regurgitation challenging. Patients with acute severe mitral regurgitation are in frank pulmonary edema and are therefore sitting upright, whereas patients with ventricular septal defect can tolerate the supine position. A soft murmur, cool extremities, increased jugular venous pressure, and an S3 are not specific to either mitral regurgitation or a ventricular septal defect.

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CHAPTER 12

Surface Electrocardiography

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

12-1. Which of the following technical errors may result in an electrocardiogram with farfield signals in lead II?

- A. Interchanging of the right arm and right leg leads
- B. Interchanging of the right arm and left arm leads
- C. Interchanging of the left arm and left leg leads
- D. Interchanging of the right arm and left leg leads
- E. Interchanging of the right leg and left leg leads

12-2. Which of the following is strongly suggestive of an *atypical* right bundle branch block (RBBB) on electrocardiogram?

- A. QRS of at least 0.12 seconds with midfinal slurring
- B. RSr' in lead V₁
- C. qRS in V₆ with S wave slurring and a positive T wave
- D. T wave with an opposite polarity to the QRS slurring
- E. QR in aVR with R wave slurring and a negative T wave

12-3. A 42-year-old woman presents to the emergency department with a 12-hour history of worsening dyspnea and weakness. She describes a recent business trip to India. Which of the following represent the *least* likely electrocardiographic sign to be observed in this clinical situation?

- A. Right bundle branch block
- B. $aVL + SV_3 > 20$ mm
- C. Sinus tachycardia
- D. Normal sinus rhythm
- E. McGinn-White pattern

12-4. A 24-year-old male with a history of palpitations presents to the emergency department. The following electrocardiographic findings may be observed in a patient with Wolff-Parkinson-White syndrome, *except*:

- A. Absence of a right bundle branch pattern in a patient with Ebstein's anomaly
- B. Preexcited atrial fibrillation
- C. A normal PR interval in the setting of a left-lateral accessory pathway
- D. Prolongation of the PR interval
- E. A narrow QRS tachycardia with a mid-RP interval

12-5. See [Figure 12-1](#). A 35-year-old woman presents with syncope. The origin of negative T waves in the inferior leads on the electrocardiogram may include which of the following?

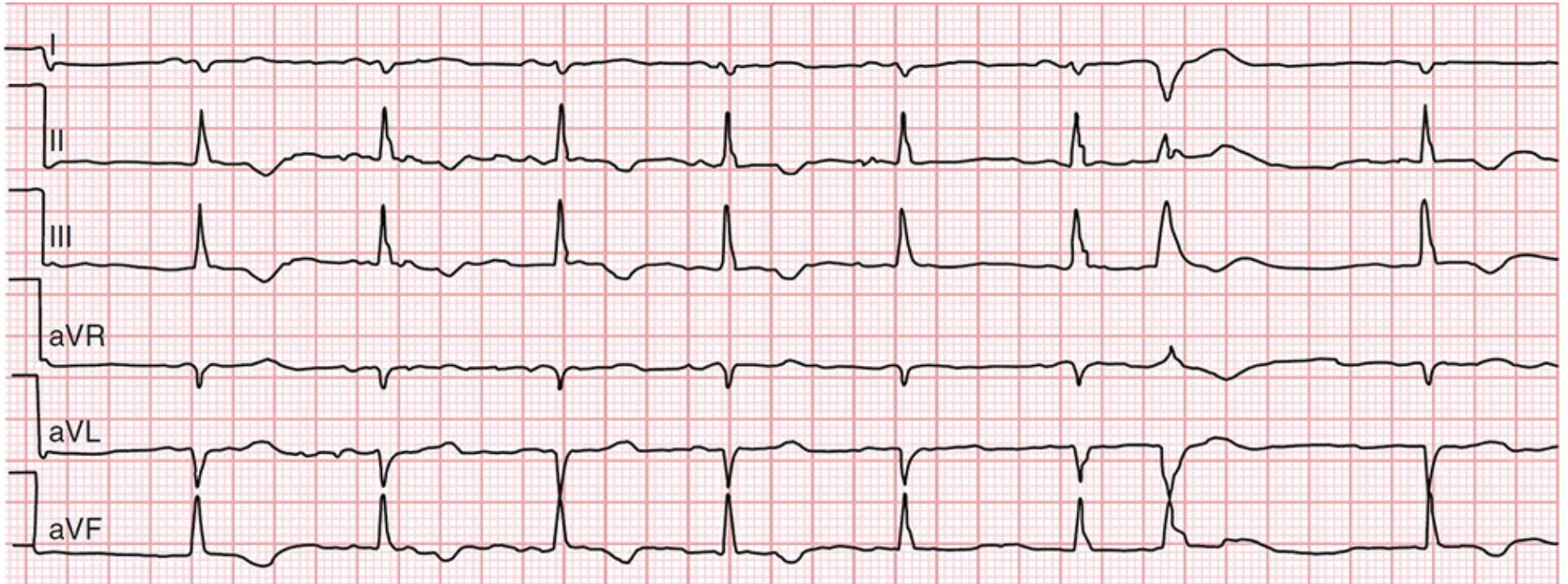


FIGURE 12-1 Electrocardiogram of a 35-year-old woman with syncope.

- A. Hyperkalemia
 - B. Left ventricular hypertrophy
 - C. Acute pericarditis
 - D. Advanced atrioventricular block
 - E. Mitral valve prolapse
- 12-6.** A 75-year-old female presents with nausea and vomiting to the emergency department. Her EKG reveals ST elevation in the inferior leads. Which of the following findings is most likely to suggest the presence of an accompanying right ventricular infarct?
- A. Negative T wave in V_4R
 - B. ST elevations in lead I
 - C. ST elevations lead II > III
 - D. ST elevations in lead V_4R
 - E. ST depression in V_4R
- 12-7.** A 35-year-old woman with a history of rheumatic fever presents to your office in consultation for intermittent palpitations and worsening dyspnea. A physical exam reveals a diastolic murmur over the apex. Thyroid studies are within normal limits. Which of the following ECG findings is *least* likely to be observed in this patient?
- A. Atrial fibrillation
 - B. Atrial tachycardia
 - C. Biphasic positive-negative p wave in V_1
 - D. R wave in V_1
 - E. T-wave inversions in II, III, aVF
- 12-8.** Causes of pathologic Q waves *not* secondary to myocardial infarction include all of the following *except*:
- A. Amyloidosis
 - B. Dilated cardiomyopathy
 - C. Wolff-Parkinson-White syndrome
 - D. Cardiac transplant
 - E. Acute myocarditis
- 12-9.** You are consulted on a 21-year-old female who requires a cardiac workup following a small right middle cerebral artery stroke. She has no other significant past medical history. On questioning, she admits to having a history of breathlessness with maximal exertion for as long as she can remember. All of the following findings may be observed on her electrocardiogram *except*:
- A. Leftward QRS axis
 - B. Left bundle branch block (LBBB)
 - C. Atrial fibrillation
 - D. Negative P waves in II, III, aVF
 - E. Presence of an rsR' in V_1 with a QRS < 0.12 seconds
- 12-10.** All of the following are associated with a dominant R in V_1 on electrocardiogram *except*:
- A. Athlete's heart

- B. Ebstein's anomaly
- C. Arrhythmogenic right ventricular dysplasia
- D. Wolff-Parkinson-White electrocardiographic pattern
- E. Lateral wall myocardial infarction

ANSWERS

- 12-1. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 12*) Interchanging of the right arm and right leg leads would result in farfield signals (diminished signals) in lead II. Interchanging of the right arm and left arm leads would result in a pattern of negative P, negative QRS, and negative T waves in lead I (and positive in aVR) (option B). A normal pattern of R wave progression from V₁ to V₆ would argue against dextrocardia in this instance if the leads were placed correctly. Interchanging left arm and left leg leads would result in reversal of leads aVL and aVF, reversal of leads I and II, and inversion of lead III (option C). Interchanging right arm and left leg leads would result in inversion of leads I, II, and III, and reversal of leads aVR and aVF (option D). Interchanging of the right and left leg leads will not result in a different ECG recording compared to one obtained with standard electrode placement (option E).
- 12-2. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 12*) The first upward deflection (R) of the QRS should always be shorter than the second upward deflection (r') in a typical RBBB. Options A, C, D, and E represent diagnostic criteria for a typical RBBB.
- 12-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 12*) The cause of the patient's dyspnea is most likely secondary to a pulmonary embolus in the context of recent travel. Commonly, the presenting ECG is normal (option D), however the most valuable diagnostic findings for a large pulmonary embolus, which are poorly sensitive but highly specific, are as follows: (1) the McGinn-White pattern (S_I, Q_{III}, negative T_{III} pattern) (option E); (2) RBBB (option A) (3) a rightward-directed QRS axis (typically > 30° to the right of its usual position); (4) negative T wave in right precordial leads; and (5) sinus tachycardia (option C), which is common except in elderly patients or in those with sinus node dysfunction. (Option B) aVL + SV₃ > 20 mm in a woman and > 28 mm in a man (Cornell voltage criterion) is highly specific for left ventricular hypertrophy, which this patient has no indication of having.
- 12-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 12*) Shortening, as opposed to prolongation of the PR interval is observed in patients with Wolff-Parkinson-White pattern on their resting electrocardiogram. The absence of an RBBB pattern in a patient with Ebstein's anomaly is highly suggestive of the presence of an accessory pathway (option A). In a recent PACES/HRS expert consensus document on the treatment of asymptomatic young WPW subjects, it is recommended that ablation should be considered in subjects between 8 and 21 years with asymptomatic WPW pattern if they have RR intervals shorter than 250 ms during atrial fibrillation due to increased risk of sudden cardiac death (option B).¹ Preexcitation suggesting antidromic conduction in WPW syndrome may still be present with a normal PR interval if the accessory pathway is far from the sinus node (eg, left lateral pathway) (option C). An orthodromic AV reciprocating tachycardia using a retrograde accessory pathway can typically present as a narrow complex tachycardia with either a mid or a long RP (option E).
- 12-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 12*) Although an infrequent finding, an electrocardiogram with mitral valve prolapse will typically reveal T-wave inversions in the inferior leads and/or V₅ and V₆. This patient had bileaflet mitral valve prolapse with moderate mitral valve regurgitation. She presented after three episodes of high-risk syncope, and she was diagnosed with malignant mitral valve syndrome. The origin of the PVC was from the anterolateral papillary muscle. Hyperkalemia classically causes peaked T waves (option A) (in contrast, hypokalemia may cause T-wave flattening). Left ventricular hypertrophy would cause a more positive than normal T wave (option B). Acute pericarditis would be more likely to show more positive T waves (option C). Advanced atrioventricular block would demonstrate tall and peaked T waves in the narrow QRS complex escape rhythm (option D).
- 12-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 12*) ST elevations in V_{4R} would be highly suggestive of a right ventricular infarct. Options A, B, C, and E are more suggestive that the left circumflex is the culprit artery.
- 12-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 12*) The patient presents with a history and a physical exam suggestive of mitral stenosis (note: a palpable S1 may be noted in mitral stenosis, thyrotoxicosis, anxiety, and in the setting of a short PR interval). Atrial fibrillation (option A), atrial tachycardia (option B), biphasic positive-negative p wave in V₁ (option C), and an R wave in V₁ (option D) are classical electrocardiographic findings of mitral stenosis. T-wave inversions in the inferior leads are not specific for mitral stenosis, but they may be observed in a patient with mitral valve prolapse (option E).
- 12-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 12*) Pathologic Q waves are not typically seen in a transplanted heart. Patients with cardiac transplant are often observed to have the P wave of both the donor and the

recipient on the same ECG. Generally the donor P wave is of a higher rate than the recipient P wave because there is no vagal control on the donor heart. A pathologic Q wave is wide (≥ 0.04 seconds) and typically exceeds 25% of the following R wave. The presence of abnormal Q waves suggests myocardial necrosis, but it may also be observed in other circumstances, such as amyloidosis (option A), dilated cardiomyopathy (option B), Wolff-Parkinson-White syndrome (option C), and acute myocarditis (option E). Other causes of pathologic Q waves include recording artifacts, normal variants (Q in aVL in a vertical heart, and Q in III in the dextrorotated and horizontal heart), QS in V₁ in septal fibrosis, emphysema, the elderly, and chest abnormalities, some types of right ventricular hypertrophy (chronic cor pulmonale) or left ventricular hypertrophy (QS in V₁-V₂ with a slow increase in the R wave through the precordial leads), left bundle branch conduction abnormalities, infiltrative processes (sarcoidosis, tumors, chronic myocarditis), coronary vasospasm, pheochromocytoma, and congenital heart diseases (coronary artery abnormalities or dextrocardia).

- 12-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 12*) The question points toward an atrial septal defect (ASD) as a potential etiology for the patient's stroke. An LBBB would not specifically be seen in the presence of an ASD (option B). A leftward QRS axis may be observed in a primum ASD, whereas a normal or rightward axis is more typical of a secundum ASD (option A). Atrial fibrillation, associated with or independent of an ASD, may be the cause of stroke in this patient (option C). Negative P waves in the inferior leads suggest a low/ectopic atrial pacemaker, which can be seen in sinus venosus/SVC defects (option D). A partial or complete RBBB, not an LBBB, may be seen in combination with an ASD (option E).
- 12-10. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 12*) An athlete's heart is not typically associated with a dominant R in V₁. Options B through E are all causes of a dominant R in V₁. Ebstein's anomaly and arrhythmogenic right ventricular dysplasia present as atypical RBBB. Other causes of a dominant R in V₁ on electrocardiogram include incorrect lead placement, chest anomalies, abnormal variants (post-term infants, scant Purkinje fibers in the anteroseptal region), typical RBBB, Brugada syndrome, and right ventricular or biventricular enlargement.

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CHAPTER 13

Electrocardiographic Exercise Testing

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 13-1.** What are the determinants of myocardial oxygen uptake?
- A. Minute ventilation and the fraction of ventilation extracted by the tissues
 - B. Cardiac output and the peripheral arteriovenous oxygen difference
 - C. Intramyocardial wall tension, contractility, and heart rate
 - D. Stroke volume and heart rate
 - E. The maximal heart rate and the maximal systolic blood pressure
- 13-2.** A 65-year-old male is referred to you for evaluation of possible coronary artery disease. He gives a 4-week history of chest discomfort with climbing two flights of stairs, where he had previously been able to climb several flights without difficulty. He denies any dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or syncope. Two weeks ago, he was started on isosorbide mononitrate 30 mg po daily, metoprolol 25 mg po twice daily, and aspirin 80 mg po daily by his primary care physician. Physical exam is within normal limits. You plan to perform an exercise stress test. Which of the following sets of instructions is *false*?
- A. Instruct the patient to hold metoprolol for at least 24 hours prior to the test
 - B. Instruct the patient to avoid vigorous exercise the day of the test
 - C. Instruct the patient to hold his morning dose of isosorbide mononitrate the day of the test
 - D. Instruct the patient to continue all medications
 - E. Instruct the patient to avoid caffeine in the event that a vasodilator stress will be performed at the same time
- 13-3.** A 48-year-old female presents to the emergency department with central chest pain and dyspnea that now occurs after walking one block. The chest pain began six months ago, but the symptoms have become more frequent and occur with even less exertion. She describes an episode of syncope without prodrome. Her family history is significant for a brother having undergone a cardiac surgery at age 52. A systolic ejection click with an associated systolic murmur is noted on exam. Serial troponins are negative. What is the next best course of action?
- A. Book an exercise stress test
 - B. Proceed with transthoracic echocardiography
 - C. Proceed with coronary angiography
 - D. Consult cardiac surgery
 - E. Start a beta blocker and discharge home with follow-up in clinic
- 13-4.** Which of the following is *not* an absolute contraindication to exercise stress testing?
- A. Severe mitral stenosis
 - B. Unstable angina
 - C. Acute pericarditis
 - D. Stable, sustained monomorphic VT
 - E. > 3 mm ST segment depression at rest
- 13-5.** Which of the following statements about exercise stress testing is *false*?
- A. The formula $MPHR = 220 - \text{age}$ results in an underestimation of maximum heart rate, particularly in older patients
 - B. The formula $MPHR = 220 - \text{age}$ was originally developed to be used for patients' exercise prescriptions
 - C. The exercise stress test may be terminated when the maximal predicted heart rate reaches 85%
 - D. Achieving either maximum effort or an ischemic endpoint is crucial for exercise testing performed with or without imaging

- E. The maximum predicted heart rate is best achieved by using the formula $MPHR = 208 - 0.7 \times \text{age}$

Questions 13-6, 13-7, and 13-8 relate to the following vignette:

A 42-year-old man with diabetes mellitus type II and dyslipidemia is referred for an exercise stress test from the emergency department. He began to complain of dull left shoulder pain 2 weeks prior to presentation. The pain has worsened in the last few days, and it is precipitated by walking up stairs. He remarks that he thinks he may have hurt his shoulder during snow shoveling 2 weeks ago. A physical exam reveals a blood pressure of 138/78 HR 84 regular, oxygen saturation 98% on room air, and respiratory rate of 14. He is afebrile. Normal heart sounds are auscultated, and no murmurs are present. Serial troponins are negative.

- 13-6.** In this patient, all of the following resting electrocardiographic findings may cause reconsideration of an exercise stress test as the primary investigation, *except*:
- A. Presence of preexcitation
 - B. Presence of an LBBB
 - C. Presence of a paced rhythm
 - D. Atrial fibrillation with a rapid ventricular response
 - E. Intraventricular conduction delay
- 13-7.** All of the following parameters should usually prompt exercise stress test termination *except*:
- A. 1 mm ST elevation in the anterior precordial leads
 - B. A decrease in the systolic blood pressure by 10 mm Hg
 - C. Patient would like to terminate the test
 - D. Isolated premature ventricular contractions
 - E. Mobitz type 1 second-degree heart block
- 13-8.** Which of the following results would constitute the worst prognosis?
- A. 1 mm of slow upsloping ST depression at 5 METS, with resolution upon termination of exercise
 - B. 0.5 mm of slow downsloping ST depression at 7 METS, with persistence into 2 minutes of recovery
 - C. 1.5 mm of horizontal ST depression at 5 METS, with resolution upon termination of exercise
 - D. 1.5 mm of horizontal ST depression at 5 METS, with persistence into 2 minutes of recovery
 - E. 1.5 mm of downsloping ST depression at 7 METS, with resolution upon termination of exercise
- 13-9.** Which of the following patients performing an exercise stress test would be identified as a moderate risk for cardiovascular death or nonfatal myocardial infarction over 5 years follow-up?
- A. A 45-year-old male performs 7 minutes on EST, limited by chest pain with 2 mm ST depressions during exercise in the inferior leads
 - B. A 55-year-old female performs 7 minutes on EST, and she stops due to fatigue with 1 mm of horizontal ST depressions into recovery in the anterior precordial leads
 - C. A 64-year-old female performs 8 minutes on EST, and she stops as a result of leg pain with 0.5 mm ST depressions in the inferior leads during exercise only
 - D. A 55-year-old female performs 4 minutes on EST, and she stops due to dyspnea, with 3 mm of horizontal ST depressions in the anterior precordial leads during exercise
 - E. A 70-year-old male performs 7 minutes on EST, limited by leg cramping, with no ST deviation
- 13-10.** Select the *false* statement about EST:
- A. Digoxin can produce ST segment depression during exercise even if the effect is not evident on the resting ECG
 - B. Exercise-induced ST segment elevation is nonspecific for the territory of myocardial ischemia and the coronary artery involved
 - C. The expected lower sensitivity and specificity traditionally observed in women may be explained by differing CAD prevalence and severity
 - D. Submaximal exercise testing in which exercise is stopped at a predetermined end point, such as a peak heart rate of 120 beats/min, 70% of MPHR, or a peak MET level of 5, can be used as a class I indication 4 to 7-plus days post-MI for evaluation of medical therapy, prognostic assessment, or development of an activity prescription
 - E. Exercise-induced ST segment depression does not localize the site of myocardial ischemia, nor does it indicate which coronary artery is involved

ANSWERS

- 13-1. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 13*) The determinants of myocardial oxygen uptake are intramyocardial wall tension (left ventricular pressure and end-diastolic volume), contractility, and heart rate (option C). Myocardial oxygen uptake can be estimated by the product of heart rate and systolic blood pressure (the double product or rate pressure product). This information is valuable clinically because exercise-induced angina often occurs at the same myocardial oxygen demand and thus double product. The higher the double product achieved, the better the myocardial perfusion and prognosis. VO_2 max is determined by the maximal amount of ventilation (volume of expired gas [VE]) moving into and out of the lung and by the fraction of this ventilation that is extracted by the tissues: $\text{VO}_2 = \text{VE} \times (\text{FiO}_2 - \text{FeO}_2)$ where VE is the minute ventilation and FiO_2 and FeO_2 are the fractional concentration of oxygen in the inspired and expired air, respectively (option A). The determinants of volume oxygen consumption [VO_2] are cardiac output and the peripheral arteriovenous oxygen difference. Because maximal arteriovenous difference behaves more or less as a constant, maximal oxygen uptake serves as an indirect estimate of maximal cardiac output (option B). The product of stroke volume and heart rate is the cardiac output (option D). The rate pressure product is the product of the maximal heart rate (bpm) and the maximal systolic blood pressure (mm Hg), and it represents the internal workload or hemodynamic response (option E).
- 13-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 13*). The exercise stress test is being performed to determine if the patient has coronary artery disease. Antianginal medications should be held to minimize their anti-ischemic impact (hold beta-blockers for 24 hours [option A] and hold nitrates and calcium channel blockers the day of the study [option C]). If medications are not held, the test sensitivity may be decreased either by the patient's medical regimen or by the fact that the ischemia was not seen at the level of exertion or double product achieved. If the test is being performed for prognostic reasons (that is, if coronary disease is known to be present), then medications do *not* need to be held. Avoiding vigorous exercise on the day of exercise testing is appropriate to enhance the patient's ability to achieve maximum exercise on the test (option B). Caffeine is a competitive antagonist of adenosine receptors and thus blocks the effect of dipyridamole, adenosine, and regadenoson. It should be withheld for at least 12 hours if there is a possibility of the patient undergoing a vasodilator stress the same day (option E).
- 13-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 13*) The patient has a probable diagnosis of a stenotic bicuspid aortic valve. Her symptoms are suggestive of a high degree of valve stenosis with possible concomitant coronary artery disease. A transthoracic echocardiogram would be the best first choice (option B). Exercise stress testing would be an absolute contraindication in a patient with possible severe aortic stenosis (option A). Proceeding directly with coronary angiography (option C) or cardiac surgery (option E) would be premature. The patient's symptoms, and particularly that of syncope, are worrisome enough to keep the patient in the hospital until at least a transthoracic echocardiogram is performed (option E).
- 13-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 13*) >3 mm ST segment depression at rest is a *relative* contraindication to exercise stress testing. Options A through D are all absolute contraindications to exercise stress testing. Other absolute contraindications include patients with acute myocardial infarction, acute myocarditis, Mobitz type 2, second or third degree heart block, known severe left main disease, acutely ill patients, patients with locomotive problems, severe aortic or other valve stenosis, acute pulmonary embolus, and uncontrolled symptomatic heart failure.
- 13-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 13*) Stopping exercise prematurely once 85% of an estimated maximal heart rate is achieved decreases exercise testing sensitivity and minimizes the opportunity to assess ischemia electrocardiographically and with adjunctive imaging (option C). Bairey and coworkers compared patients undergoing exercise myocardial perfusion imaging with a normal perfusion scan relative to whether they achieved 85% of MPHR. The annual event rate of death, nonfatal MI, or late revascularization was 1.9% for those who reached $\geq 85\%$ MPHR compared to 8.6% for those who achieved $< 85\%$.¹ The formula of $\text{MPHR} = 220 - \text{age}$ results in an underestimation of maximum heart rate, particularly in older patients (option A), and was originally developed for use in patients' exercise prescriptions (option B). Further, achieving either maximum effort or an ischemic endpoint is crucial (option D). In a meta-analysis of 351 studies involving 18,712 patients, Tanaka and colleagues found that the formula of $208 - 0.7 \times \text{age}$ best predicted the maximum heart rate.² The formula was predictive in men and women and independent of habitual activity level (option E).
- 13-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 13*) Exercise stress testing will be difficult to interpret in the presence of a delta wave (option A), LBBB (option B), ventricular pacing (option C), > 1 mm of resting ST depressions, or any atrial arrhythmia with an uncontrolled ventricular response (option D). Accompanying myocardial perfusion imaging, stress echocardiography, or calcium scoring would be other tests of choice.
- 13-7. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 13*) The 2002 ACC/AHA guidelines state that exercise should be terminated when premature ventricular contractions occur in pairs with increasing frequency as exercise increases, or when at least three-beat ventricular tachycardia occurs. Other causes for termination include, but are not limited to: ST elevation > 1 mm in precordial or inferior leads that do not have a resting Q wave; onset of Mobitz type 1 or 2 second-degree or third-degree heart block; any decrease in systolic blood pressure during exercise, particularly if accompanied by another indication of ischemia; ST depression ≥ 2 mm; atrial tachycardia, atrial fibrillation, or atrial flutter; patient dyspnea; fatigue or lightheadedness; moderate musculoskeletal pain; patient becomes pale or clammy; and anginal pain increasing to moderate severity.

- 13-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 13*) The ACC/AHA 2002 exercise testing guidelines classify an abnormal result as ≥ 1 mm of horizontal or downsloping ST depression. In the 2013 AHA scientific statement on exercise standards for testing and training, ≥ 1 mm of slow upsloping is defined as equivocal. There is sufficient evidence to conclude, however, that slow upsloping ST depressions of ≥ 1.5 mm should be included as a criterion for a positive exercise test in addition to the conventional criterion of ≥ 1 mm of horizontal or downsloping ST depression.³ The earlier during exercise that ST depression occurs, and the lower the rate pressure product of this depression, and the longer it lasts during recovery, the more severe the coronary artery disease, as manifested by the incidence of multivessel and left main disease on coronary angiography.
- 13-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 13*) This patient's Duke Treadmill score is 2, which falls into the moderate risk category. Duke Treadmill Score (DTS) = Exercise time in minutes on the standard Bruce protocol – 5 \times ST deviation (depression or elevation measured in mm in the lead with the greatest degree of ST deviation) – 4 \times exercise angina index, where 0 = no angina on the treadmill, 1 = angina occurred, 2 = angina caused termination of exercise. A DTS of +5 or greater constitutes the lowest risk; a DTS of +4 to –10 constitutes a moderate risk; and a DTS of –11 or lower constitutes the highest risk. Option A has a DTS of –11 (high risk). Option C has a DTS of 5.5 (low risk). Option D has a DTS of –11 (high risk). Option E has a DTS of 7 (low risk).
- 13-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 13*) Unlike ST segment depression, ST segment elevation during exercise in contiguous leads with an R wave localizes to the coronary artery involved. Although ST depression is consistent with subendocardial ischemia, ST elevation is most consistent with transmural ischemia. Options A and C through E are true.

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CHAPTER 14

Cardiac Radiography

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 14-1.** Radiographic assessment of the lung can often reflect the underlying pathophysiology of diseases of the heart. Which of the following statements regarding the normal radiographic appearance of the pulmonary vasculature of an upright human being is *false*?
- A. The pressure differential between the apex and the base of the lung is approximately 22 mm Hg in adult men
 - B. The number of vessels and their length are more important than their caliber
 - C. Pulmonary blood volume can be assessed by comparing the size of the pulmonary artery with that of the accompanying bronchus
 - D. There is caudalization of the pulmonary vascularity because of gravity
 - E. None of the above
- 14-2.** A 55-year-old man, with no prior cardiac history, presented to the emergency department complaining of acute dyspnea. His chest x-ray revealed cephalad redistribution of the pulmonary vascularity. In which of the following conditions does cephalization *not* occur?
- A. Mitral stenosis
 - B. Pulmonic stenosis associated with ventricular septal defect
 - C. Aortic stenosis
 - D. Left ventricular (LV) failure
 - E. Severe mitral regurgitation (MR)
- 14-3.** A 25-year-old immigrant, with no prior medical history, is referred to your clinic for further evaluation of an abnormal chest radiography, which was discovered incidentally after a positive tuberculin skin test (Mantoux test). Otherwise she had no chest pain, dyspnea, or other specific signs or symptoms. Her chest x-ray is illustrated in [Figure 14-1](#). Which of the following is the most likely radiographic diagnosis?



FIGURE 14-1 The heart is normal; however, the cardiac contour is markedly abnormal with elevation of the heart and in particular the cardiac apex. There is a broad band of lucency between the inferior cardiac border and the left hemidiaphragmatic silhouette, caused by normal left lung parenchyma beneath the heart that moves into place below the heart.

- A. Congenital absence of the pericardium
- B. Late presentation of tetralogy of Fallot
- C. Left ventricular aneurysm
- D. Severe rheumatic mitral stenosis with tricuspid regurgitation
- E. None of the above

14-4. A 64-year-old man, with a 40 pack-year history of tobacco smoking, was admitted to the emergency department with a chief complaint of progressive worsening dyspnea on exertion. A chest radiography was performed, illustrated in [Figure 14-2](#), and was reported as overaeration of the lungs, centralized flow pattern, and a small heart size. Besides chronic obstructive pulmonary disease, which of the following conditions may also present with a smaller-than-average heart on a chest radiography?

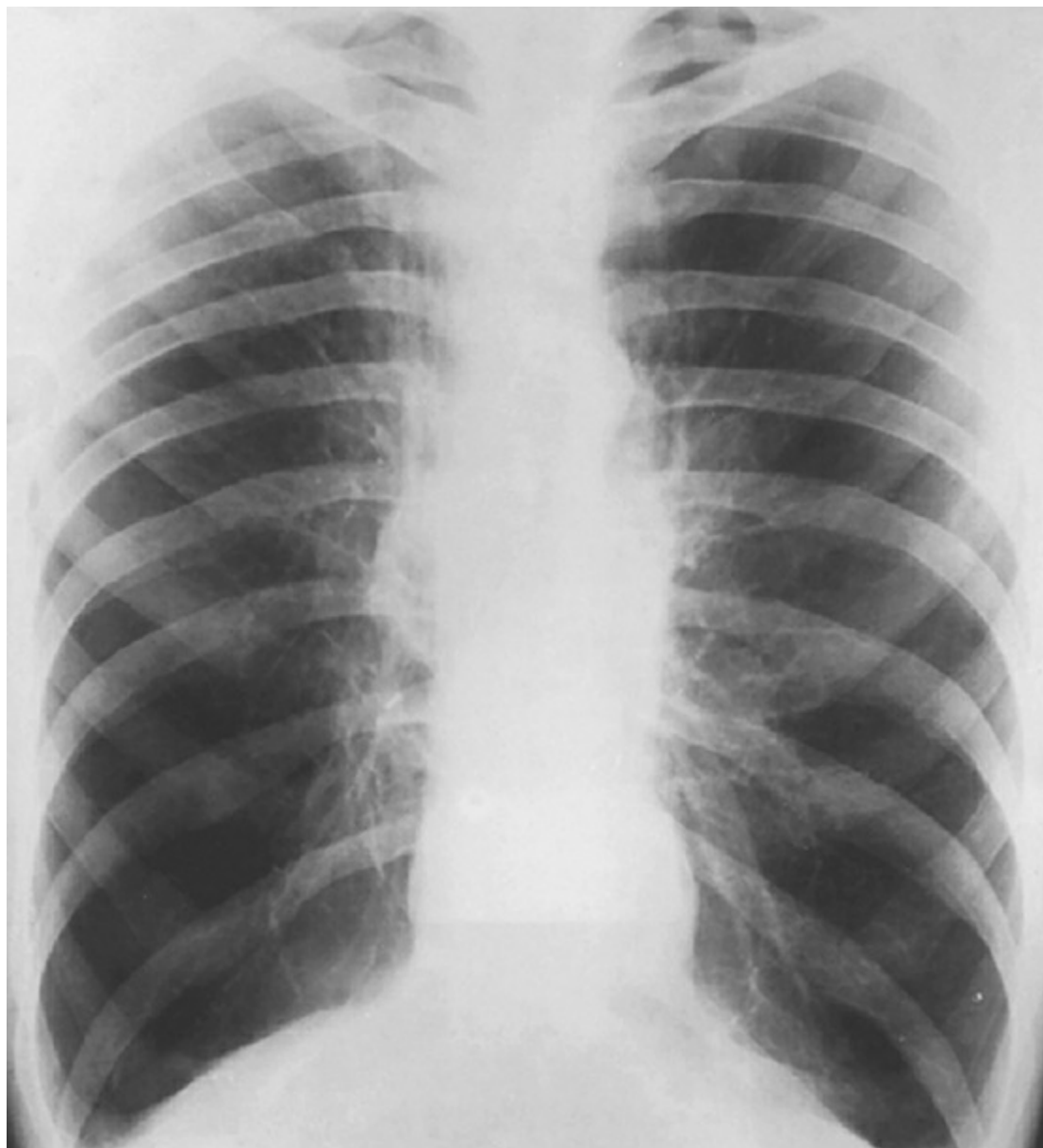


FIGURE 14-2 Severe obstructive emphysema showing overaeration of the lungs, centralized flow pattern, and a small heart size.

- A. Addison disease
- B. Anorexia nervosa
- C. Starvation
- D. None of the above
- E. All of the above

14-5. A 75-year-old woman underwent a routine preoperative chest radiography prior to surgery for a carcinoma of the sigmoid colon. Her past medical history is significant for type 2 diabetes and arterial hypertension. Her chest x-ray shows linear calcifications within the aortic arch knob. Which of the following statements regarding radiologically detectable calcification in the heart is *false*?

- A. Calcification of the coronary artery is almost always associated with flow-limiting luminal stenosis
- B. Calcification of the coronary artery is almost always atherosclerotic in nature
- C. The extent of valvular calcification tends to be proportionate to the severity of the valve stenosis
- D. Mitral annular calcification is rarely indicative of significant disease
- E. None of the above

14-6. A 25-year-old man sustained a severe stab wound to the left anterior hemithorax while attempting to break up a domestic fight. On presentation at the emergency department, he was hemodynamically stable. After a left-sided thoracostomy tube was inserted, the patient had a chest x-ray, which showed abnormal lucent areas around the heart. Which of the following conditions may cause abnormal lucent areas in and around the heart?

- A. Displaced subepicardial fat stripes
- B. Pneumopericardium
- C. Pneumomediastinum
- D. None of the above
- E. All of the above

14-7. A 44-year-old woman with no prior medical history presented to the emergency department complaining of chest pain and palpitations. The admitting physician incidentally noted that the patient had heart sounds on the right side of the chest with no added sounds. A chest x-ray was performed and is illustrated in [Figure 14-3](#). Which of the following diagnoses is consistent with the chest radiography findings?

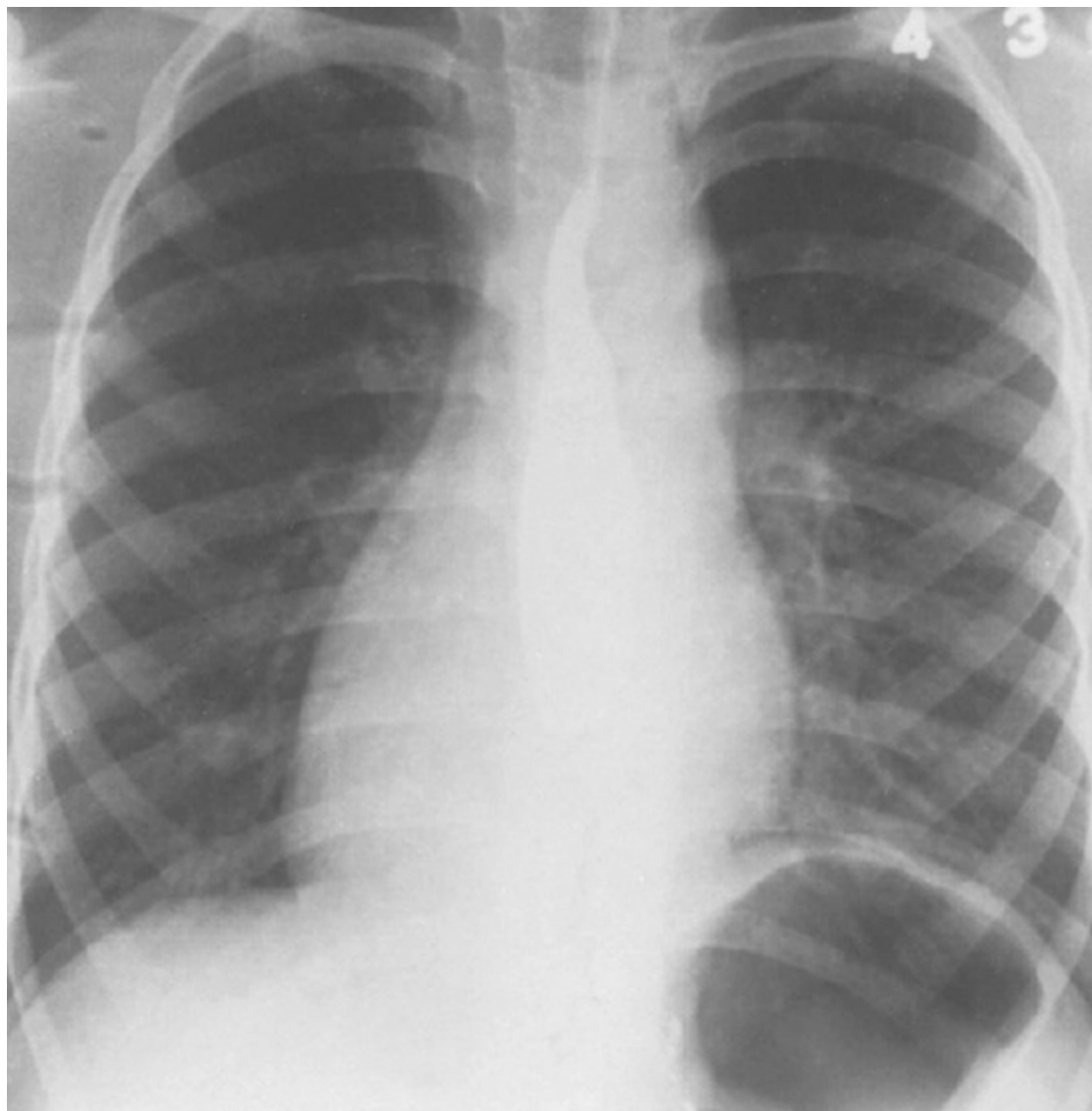


FIGURE 14-3 Note that the aortic arch and the stomach air bubble are both on the left and the apex of the ventricles is pointing to the right inferiorly. This patient had the typical combination of congenitally corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis. He was cyanotic. The pulmonary vascularity appears decreased.

- A. Dextrocardia with situs inversus
- B. Dextrocardia with situs solitus
- C. Levocardia with situs inversus
- D. Levocardia with situs solitus
- E. Cardiac malpositions with situs ambiguus

14-8. The abnormal size and distribution of both the pulmonary and systemic vessels may give important clues to the presence of certain conditions. In which of the following conditions is the prominence of the pulmonary trunk reliably correlated with the degree of enlargement of the right ventricle (RV)?

- A. Tetralogy of Fallot
- B. Idiopathic dilatation of the pulmonary artery
- C. Patent ductus arteriosus
- D. Straight-back syndrome
- E. None of the above

14-9. A 47-year-old man was admitted to the emergency department complaining of increasing fatigue and dyspnea on exertion. His past medical history is significant for dyslipidemia and poorly controlled hypertension despite being on three antihypertensive medications, including a diuretic. Physical examination was significant for bilateral femoral pulses that were palpable but weak and delayed, as compared with the brachial pulses. The magnified view of the left upper thorax of the chest radiography is illustrated in [Figure 14-4](#). With regard to the radiographic appearance, which of the following statements is *true*?

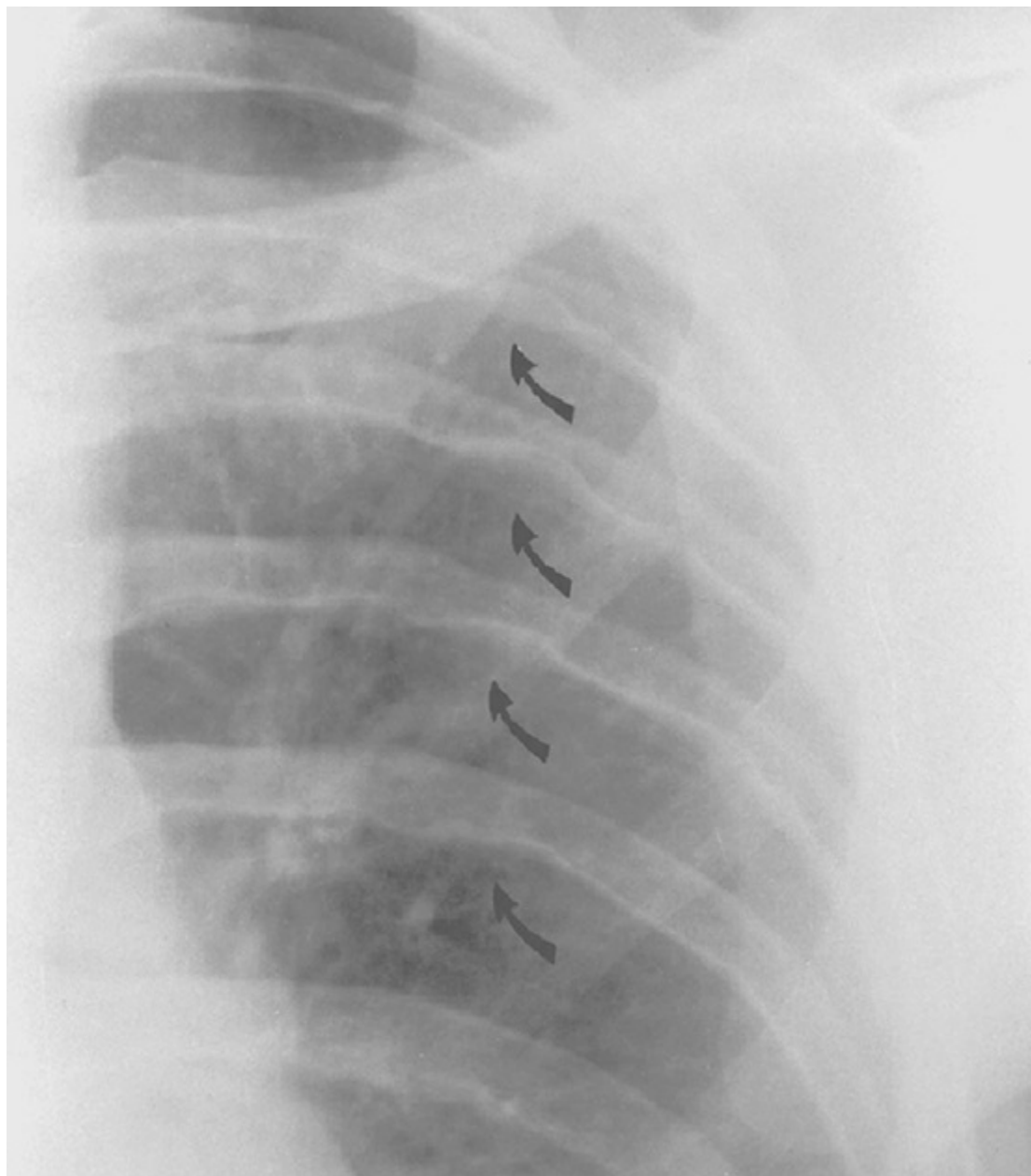


FIGURE 14-4 Magnified view of the left upper thorax showing multiple areas of rib notching (arrows).

- A. Rib notching provides important clues to the diagnosis of coarctation of the aorta
- B. Notching of the ribs has many origins
- C. Superior vena cava (SVC) syndrome can produce a similar radiographic appearance
- D. Neurofibromatosis can produce rib notching
- E. All of the above

14-10. Cardiac fluoroscopy explores the dynamic features of the heart that are discernible in motion. Which of the following statements regarding cardiac fluoroscopy is *false*?

- A. It has been largely displaced by other imaging techniques for the precise evaluation of cardiac size and function
- B. It can assess the function of radiodense and echodense prosthetic valves during cardiac catheterization
- C. It can be used to guide the positioning of pacemakers or ICDs in the cardiac catheterization laboratory
- D. It is routinely used during transcatheter aortic valve implantation to guide the deployment of the prosthesis
- E. None of the above

ANSWERS

14-1. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 14*) In the evaluation of pulmonary vasculature, the caliber of the vessels is more important than the length or the number (option B). As long as the pulmonary blood flow pattern remains normal, with a greater amount of flow to the bases than to the apices, the volume of the flow is proportional to the caliber of the pulmonary arteries. Options A, C, and D are correct.

14-2. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 14*) Patients with pulmonic stenosis and associated ventricular septal defect (VSD) often show decreased pulmonary vascularity with smaller and shorter pulmonary arteries and veins and more radiolucent lungs. Cephalization tends to occur instead in (1) left-sided obstructive lesions—for example, mitral valvular or aortic valvular stenosis (options A and C); (2) LV failure (option D)—for example, coronary heart disease or cardiomyopathies; and (3) severe MR even before pump failure of the LV occurs (option E).¹ Option B is therefore the correct answer.

14-3. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 14*) An elevated cardiac silhouette with lucency between the

inferior cardiac border and the left hemidiaphragmatic silhouette is characteristic of congenital absence of the pericardium (option A). A coeur en sabot, a “boot-shaped heart,” is characteristic of tetralogy of Fallot (option B). A bulge along the left cardiac border with a retrosternal double density is virtually diagnostic of LV aneurysm (option C). A markedly widened right cardiac contour with a straightened left cardiac border is often seen in patients with severe MS leading to tricuspid regurgitation (option D).

- 14-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 14*) The cardiothoracic ratio remains the simplest yardstick for assessing cardiac size. A smaller-than-average heart is encountered in patients with chronic obstructive pulmonary disease, Addison disease (option A), anorexia nervosa (option B), and starvation (option C). However, an abnormally small heart size is difficult to define except retrospectively after successful treatment of the underlying pathology.
- 14-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 14*) Any radiologically detectable calcification in the heart may be clinically important. In general, the heavier the calcification, the more significant it becomes; however, calcification does not imply luminal stenosis, and oftentimes calcification visualized in the coronary arteries is not obstructive (option A). Mitral annular calcification, a commonly encountered cause of cardiac calcification, is rarely indicative of significant disease (option D), but it has been associated with an increased risk of atherosclerotic cardiovascular disease.² The extent of valvular calcification tends to be proportionate to the severity of the valve stenosis regardless of the other radiographic signs of the disease (option C).³⁻⁶ Calcification of the coronary artery is almost always atherosclerotic in nature (option B).
- 14-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 14*) The abnormal lucent areas in and around the heart include (1) displaced subepicardial fat stripes caused by effusion or thickening of the pericardium (option A), (2) pneumopericardium (option B), and (3) pneumomediastinum (option C). Pneumomediastinum is differentiated from pneumopericardium in that the former shows a superior extension of the air strip beyond the confines of the pericardium.
- 14-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 14*) Dextrocardia with situs solitus represents an anomaly with normal situs but a right-sided heart. Radiographically, normal situs (situs solitus) is a certainty when both the aortic knob and the gastric air bubble are on the left side. Situs solitus also means that both the abdominal viscera and the atria are in the normal positions. Dextrocardia with situs inversus indicates the mirror image of normal (option A). Levocardia with situs inversus is a mirror image of dextrocardia with situs solitus (option C). Levocardia with situs solitus is entirely normal (option D). In Cardiac malpositions with situs ambiguus, the patient's heart can be on either the left or right side, but the site is ambiguous because the aortic arch and the stomach are not on the same side (option E).
- 14-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 14*) Prominence of the pulmonary trunk is a reliable secondary sign of RV enlargement, with the following exceptions: (1) Tetralogy of Fallot with RV hypertrophy but pulmonary trunk hypoplasia (option A); (2) idiopathic dilatation of the pulmonary artery (option B); (3) patent ductus arteriosus with dilated pulmonary trunk but normal RV size (option C); and (4) straight-back syndrome (option D), pectus excavatum, and scoliosis with narrowed AP diameter of the chest. Under the latter conditions, the heart is compressed, displaced, and rotated to the left, giving rise to a falsely enlarged pulmonary artery.
- 14-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 14*) Rib notching provides important clues to the diagnosis of coarctation of the aorta (option A).^{7,8} Notching of the ribs has many origins (option B). Basically, any of the three major intercostal structures can enlarge, compress, and erode the lower borders of the ribs, producing areas of notching. They are intercostal arteries, veins, and nerves. Coarctation of the aorta represents the most common cause of rib notching as a result of dynamic dilatation and tortuosity of the arteries. SVC syndrome can produce a similar radiographic appearance (option C), albeit through long-standing venous dilation. Neurofibromatosis also can produce rib notching through the compressive effect of numerous intercostal neurofibromas (option D).
- 14-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 14*) Cardiac fluoroscopy has been largely displaced by other imaging techniques (option A), particularly two-dimensional echocardiography, MRI, and CT, and its use is limited to the cardiac catheterization laboratory, where it can assess the function of radiodense and echodense prosthetic valves (option B) and can guide the positioning of pacemakers or ICDs (option C). With the emergence of transcatheter aortic valve replacement therapy, cardiac fluoroscopy has experienced a resurgence at some centers, where it is commonly used to guide the positioning of the prosthesis (option D).

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CHAPTER 15

Echocardiography

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 15-1.** High-quality echocardiographic images require optimal resolution, that is, the ability to distinguish two individual objects separated in space. Which of the following will *not* yield high-resolution images?
- A. Short wavelengths
 - B. High-frequency signal
 - C. Low-frequency signal
 - D. Small beam width
 - E. All of the above
- 15-2.** There has been a great deal of interest in using mitral inflow velocity patterns to evaluate left ventricular diastolic properties. Which of the following variables is *not* capable of influencing transmitral filling velocities?
- A. Age
 - B. Heart rate
 - C. Respiration
 - D. Position of the Doppler sample volume
 - E. None the above
- 15-3.** A 55-year-old woman with no prior cardiac history was admitted to the emergency department complaining of a 6-month history of dyspnea. On physical examination, she had jugular venous distension, distended abdomen secondary to hepatomegaly and tense ascites, severe bilateral lower limbs pitting edema, and an S3 gallop. After an initial management she was referred to the cardiologist, who performed an echocardiography, and some of the images are illustrated in [Figure 15-1](#). Based on the echo's findings, which of the following is the most likely diagnosis?

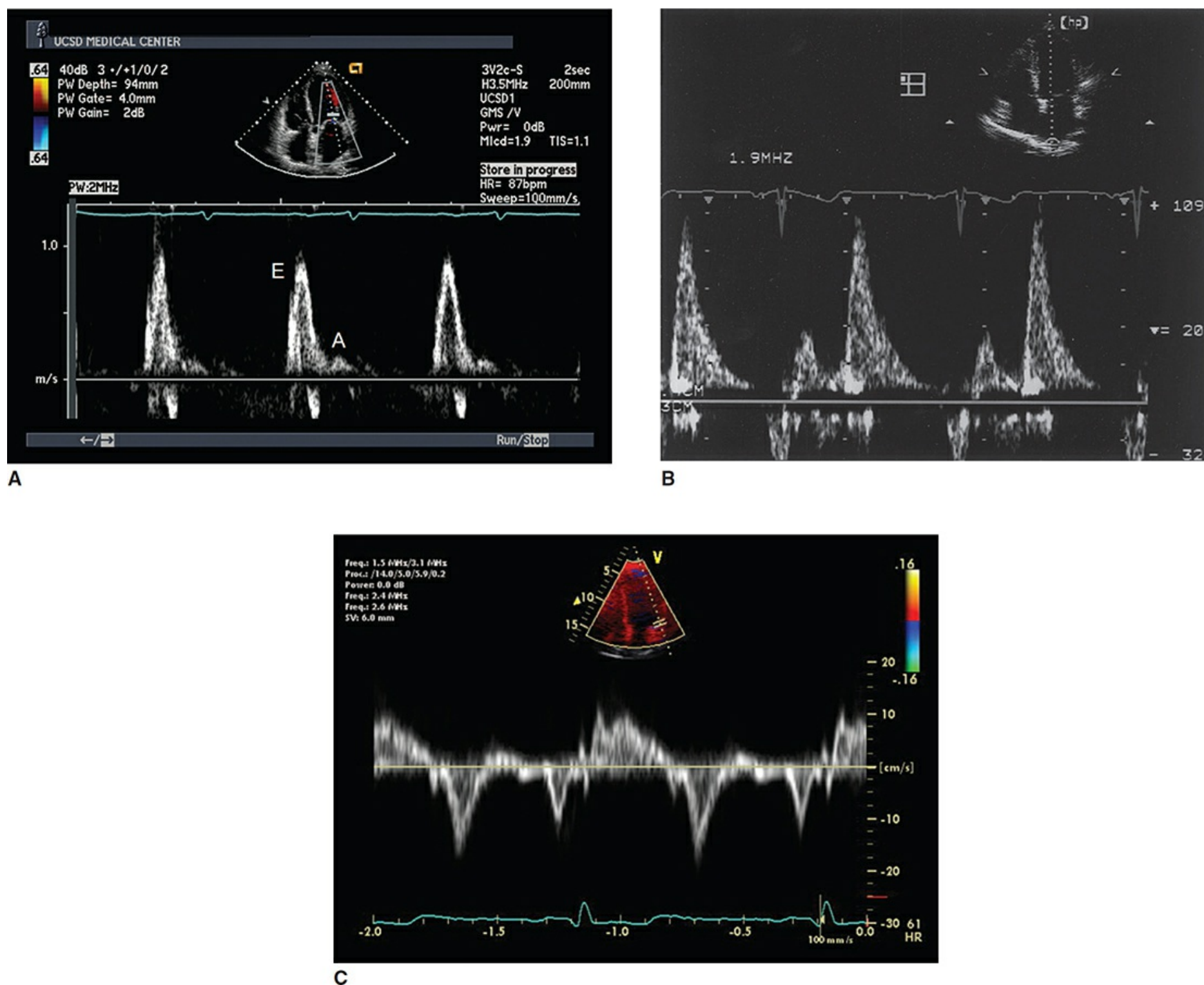


FIGURE 15-1 (A) Pulsed-wave Doppler (PWD) tracing. (B) PWD recording of pulmonary venous flow. The S wave is small, whereas the D wave is prominent. (C) Tissue Doppler recording of lateral mitral annular motion (apical transducer position). Peak early diastolic annular velocity is 17 cm/s.

- A. Constrictive pericarditis
- B. Amyloid-induced cardiomyopathy
- C. Hypereosinophilic cardiomyopathy
- D. Endomyocardial fibrosis
- E. Idiopathic restrictive cardiomyopathy

15-4. A 54-year-old woman with no prior cardiac history was admitted to the emergency department complaining of a 2-week history of progressive chest discomfort and dyspnea. On physical examination, she had a 3/6 holosystolic murmur radiating to the axilla. The initial blood tests, ECG, and chest radiography were all unremarkable. A transthoracic echo showed mitral valve prolapse with a flail posterior leaflet. Transesophageal echo was performed, and some of the images are illustrated in [Figure 15-2](#). Measurements derived from the size of the turbulent jet recorded by color Doppler are often used in clinical practice to assess the severity of mitral regurgitation. Which of the following technical factors *cannot* influence jet size?

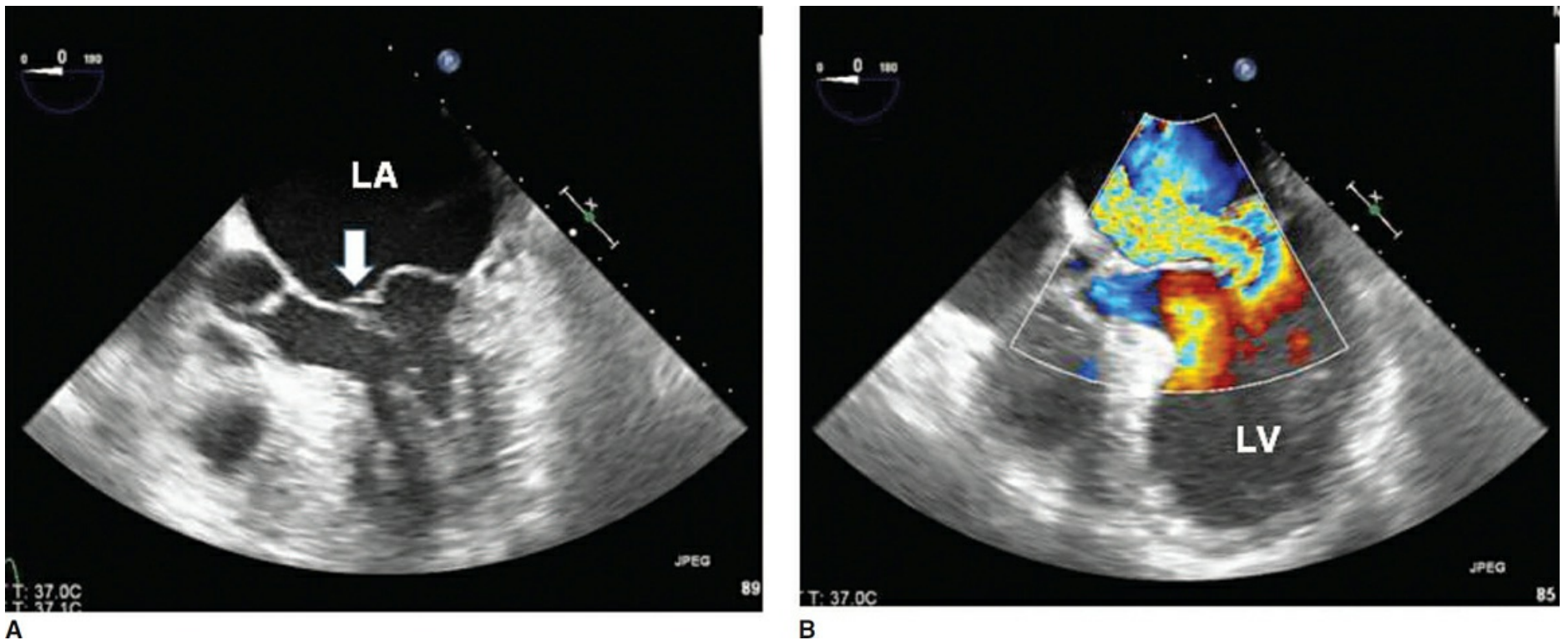


FIGURE 15-2 Transesophageal echocardiography image (five-chamber view) demonstrating a flail posterior leaflet of the mitral valve (arrow), and the corresponding color Doppler showing severe mitral regurgitation into the left atrium (LA). LV, left ventricle.

- A. Instrument gain
- B. Angle of incidence of the interrogating beam
- C. Frequency and pulse repetition rate of the transducer
- D. The temporal sampling rate
- E. None of the above

15-5. An 11-year-old woman was referred to the cardiology clinic for further evaluation of a diastolic murmur. Her past medical history was significant for a surgically closed patent ductus arteriosus at the age of 7 and recurrent chest infections since she was one year old. On general inspection, she appeared thin and slender, and she had an anterior chest deformity as well as a disproportionately long arm span compared to her height. An echo was performed, and a parasternal long-axis view is illustrated in [Figure 15-3](#). Which of the following conditions is the most likely underlying cause associated with this patient's aortic regurgitation (AR) murmur?

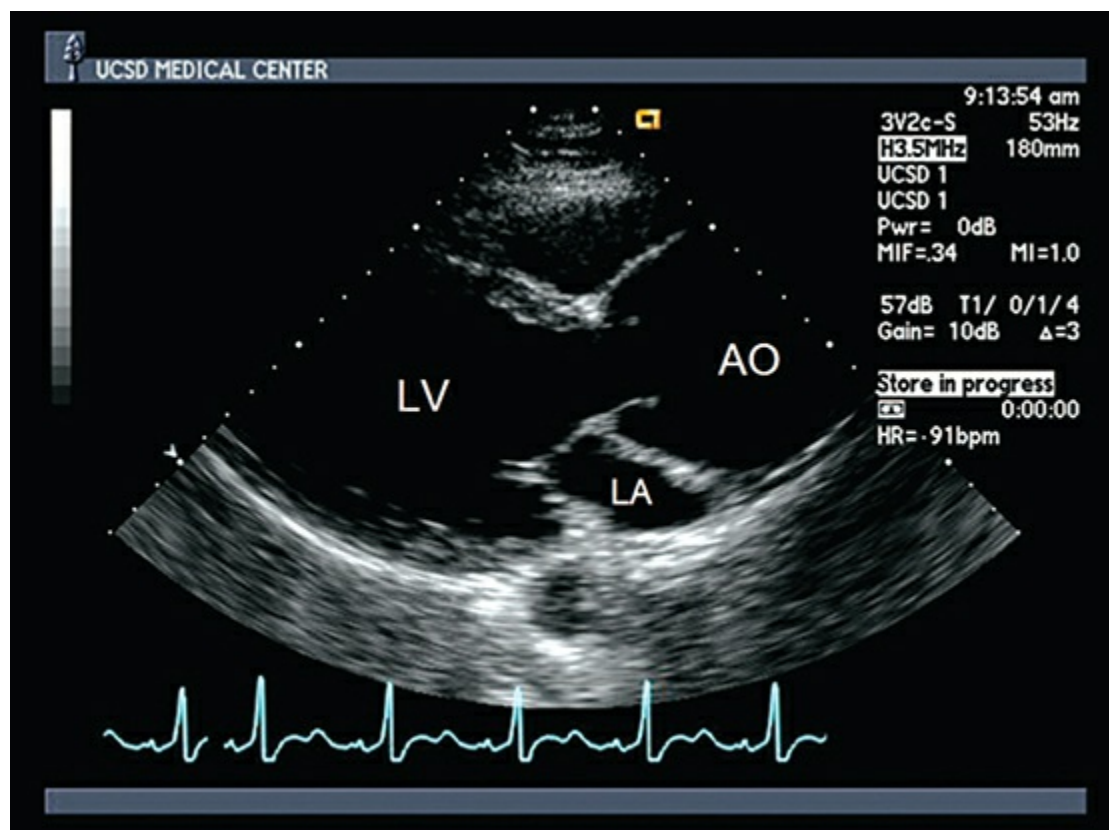


FIGURE 15-3 Parasternal long-axis view. AO, Aorta; LA, left atrium; LV, left ventricle.

- A. Marfan syndrome
- B. Sinus of Valsalva aneurysm
- C. Supravalvular aortic stenosis
- D. Coarctation of the aorta
- E. None of the above

15-6. A 92-year-old man with a prior history of dyslipidemia, type 2 diabetes, and hypertension was admitted to the emergency department complaining of dyspnea and chest pain. On physical examination, he had a grade 1/6 systolic murmur. An echo was performed, and a continuous-wave Doppler (CW) tracing (from the apical transducer position) through the aortic valve

is illustrated in Figure 15-4. Which of the following factors is *not* a potential source of error in the estimation of the transvalvular aortic gradient by CW Doppler recordings?

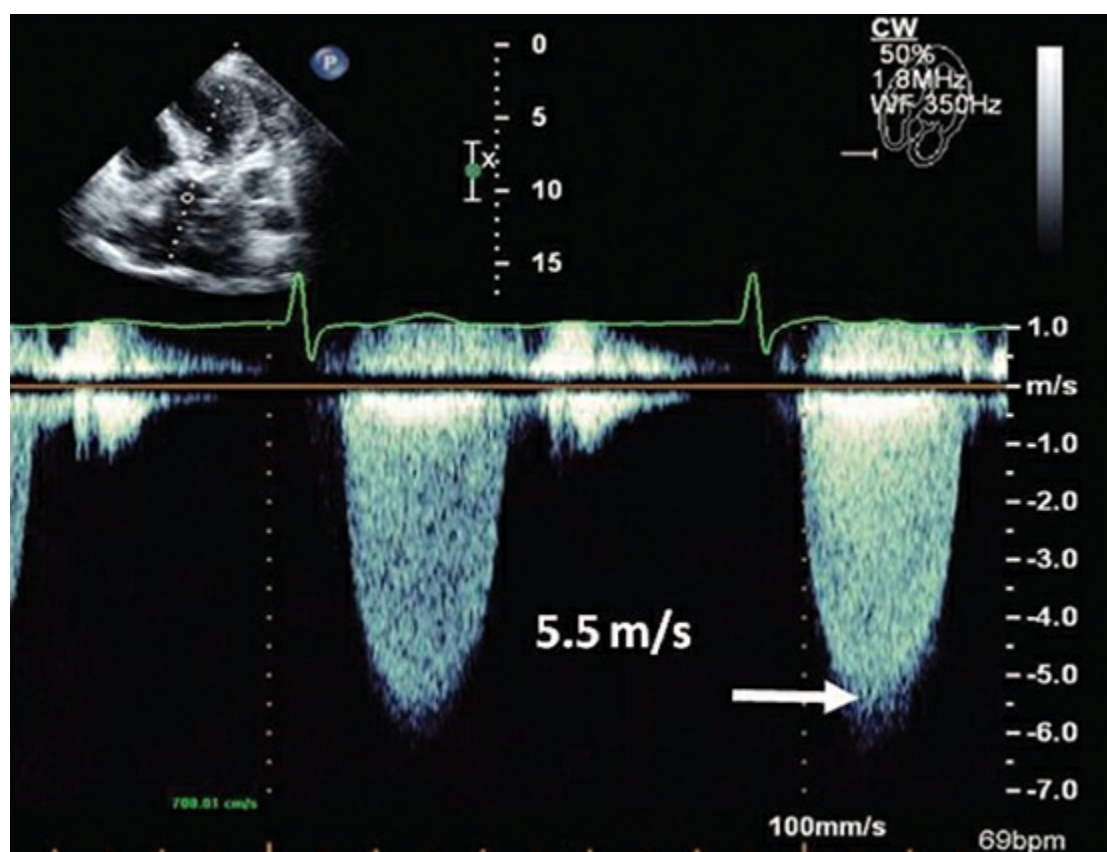


FIGURE 15-4 Continuous-wave Doppler tracing (from the apical transducer position) through the aortic valve in a case of severe aortic stenosis. The peak systolic velocity is 5.5 m/s, corresponding to a maximal instantaneous gradient of 121 mm Hg; the mean gradient is 80 mm Hg.

- A. Angle of incidence of the interrogating beam greater than 20 degrees
- B. Narrow ascending aorta
- C. Concomitant dynamic LV outflow obstruction
- D. None of the above
- E. All of the above

15-7. A 35-year-old man with no known past medical history was admitted to the emergency department complaining of a 2-day history of acute dyspnea. Upon further questioning, the patient had not been feeling well for the past 2 weeks with fever, malaise, and headaches. On physical examination, he had a diastolic murmur, best heard at the left sternal border, which was confirmed to be AR on transthoracic echo. The patient subsequently underwent a transesophageal echo, and some images are illustrated in Figure 15-5. Which of the following is the most likely cause of this patient's AR?

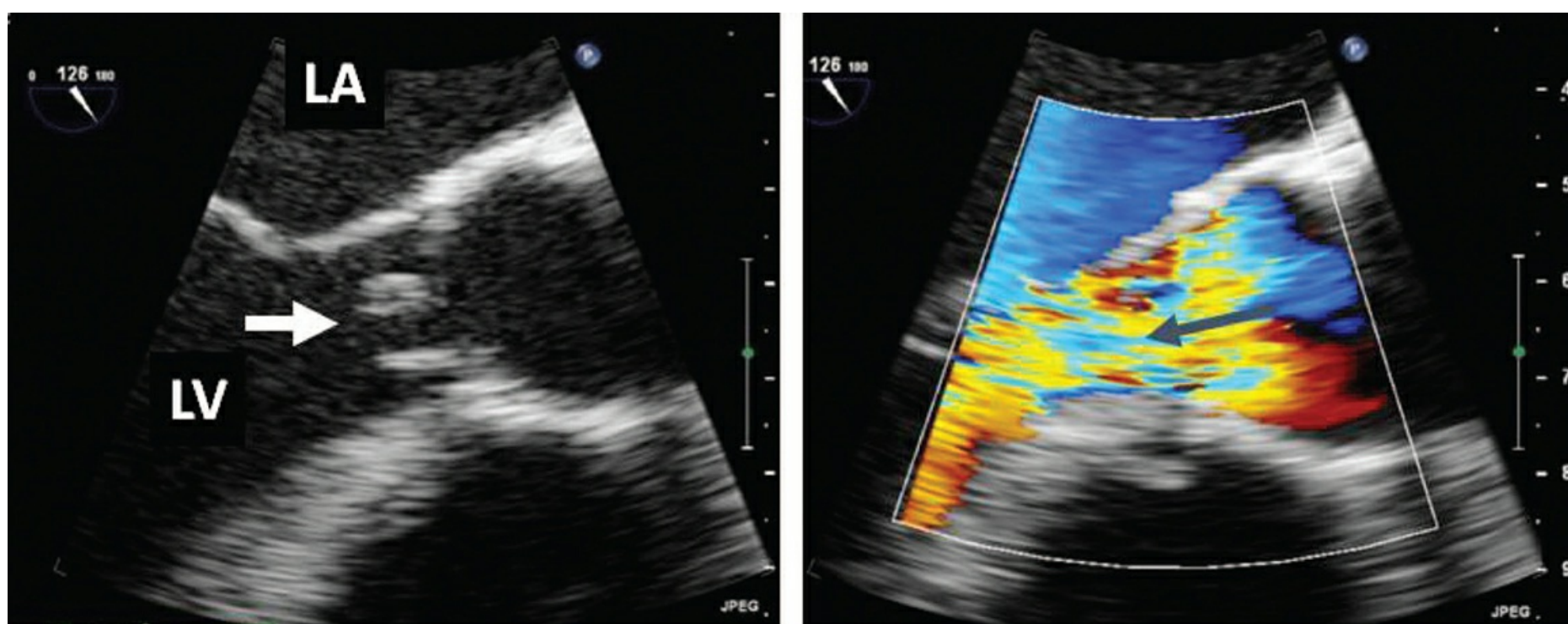


FIGURE 15-5 Transesophageal view depicting the anomaly (white arrow). Color Doppler shows severe aortic regurgitation, with the color jet occupying all of the left ventricle outflow tract. LA, left atrium; LV, left ventricle.

- A. Bicuspid aortic valve
- B. Aortic dissection
- C. Aortitis secondary to vasculitis
- D. Aortitis secondary to syphilis
- E. Infectious endocarditis

15-8. A 19-year-old man with no personal or family history of sudden cardiac death was admitted to the emergency department following a collapse while playing soccer. On cardiac auscultation, there was a grade 3/6 systolic murmur best heard over the apex. After unremarkable blood tests, ECG, and chest radiography, an echo was performed. An apical four-chamber view is illustrated in [Figure 15-6](#). In which of the following conditions does systolic anterior motion of the mitral valve (SAM) *not* occur?

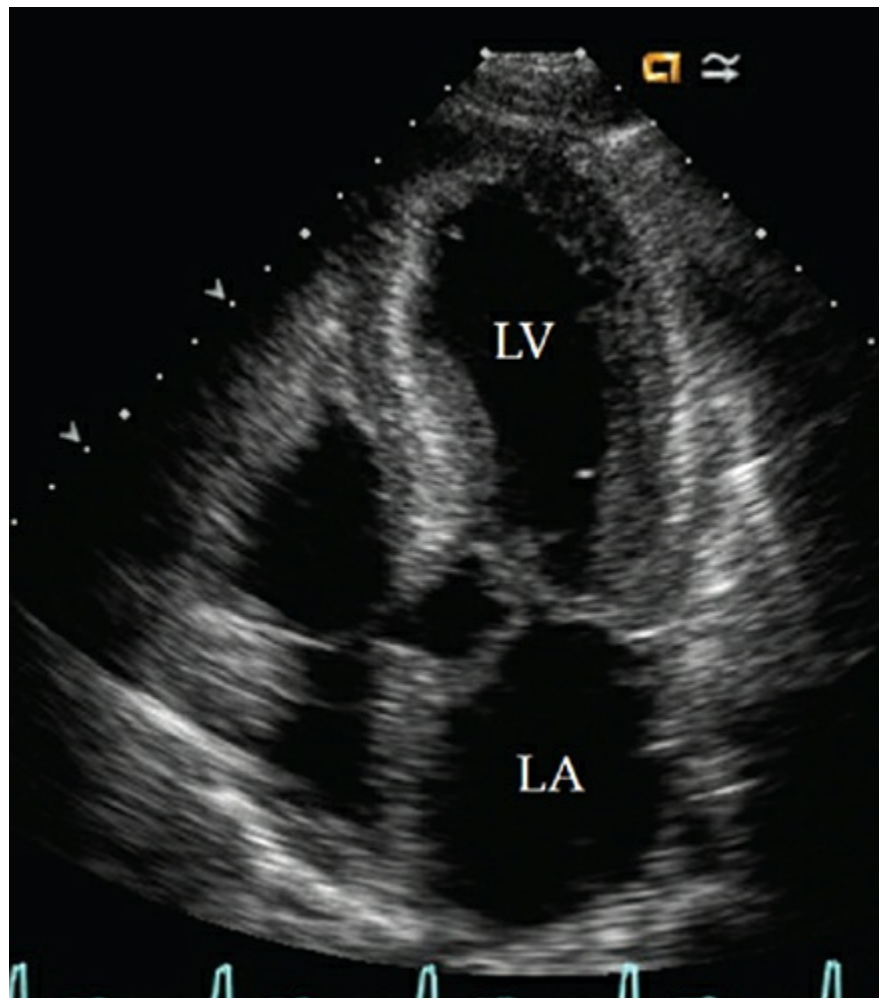


FIGURE 15-6 Apical four-chamber view during systole, demonstrating systolic anterior motion of the mitral valve. LA, left atrium; LV, left ventricle; RA, right atrium.

- A. Hypertrophic cardiomyopathy (HCM)
- B. Anemia
- C. Dehydration
- D. Following mitral annuloplasty surgery with a rigid ring
- E. None of the above

15-9. An asymptomatic 47-year-old man with a recent history of anterior STEMI was referred to the cardiology clinic by his family doctor because of a persistent ST-segment elevation in the anterior leads. An echo was performed, and an apical four-chamber view is illustrated in [Figure 15-7](#). Based on the echo's findings, which of the following is the most likely diagnosis?

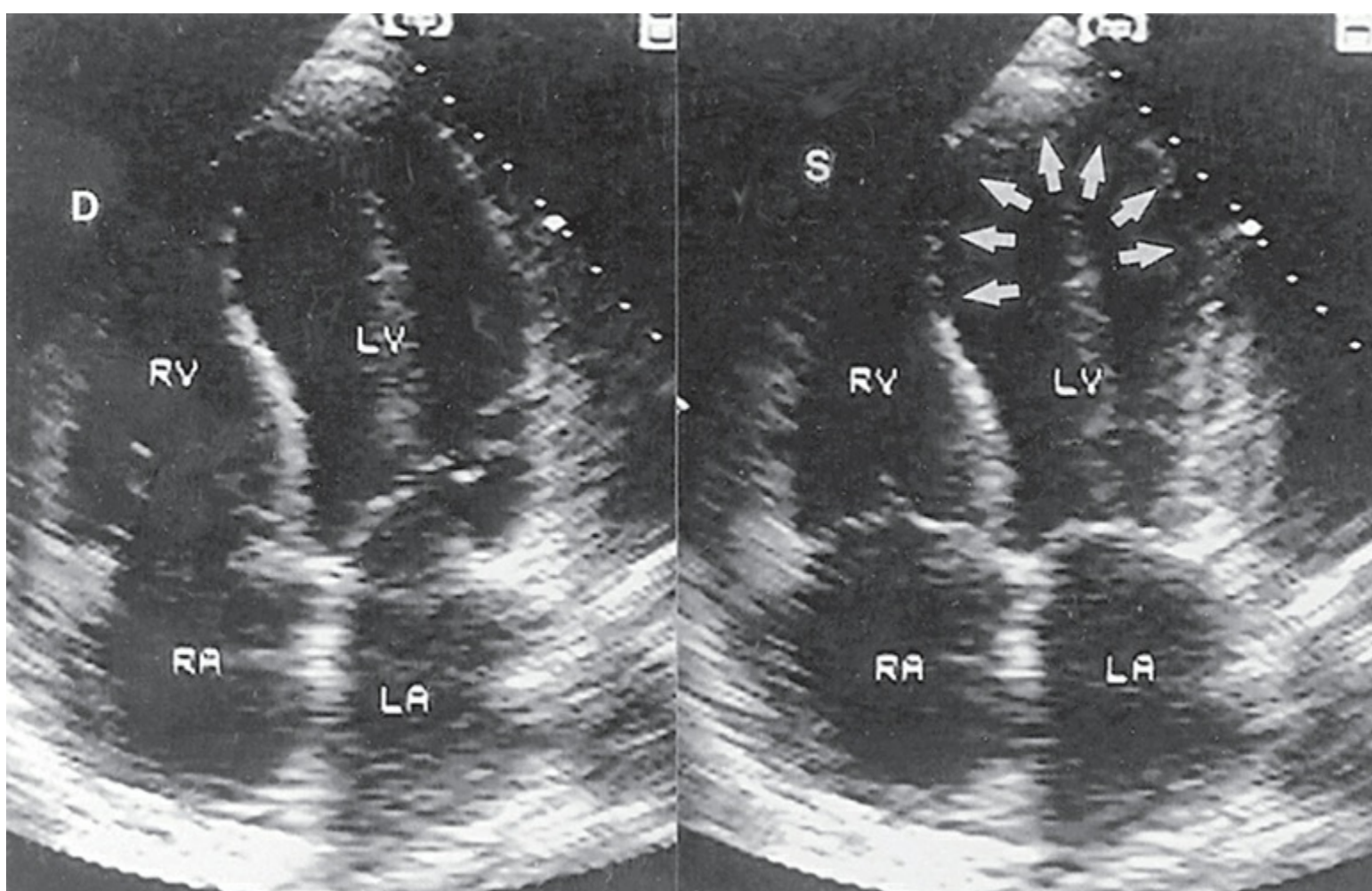


FIGURE 15-7 Apical four-chamber view. Diastole (D) is displayed on the left, systole (S) on the right. During systole, the base of the ventricle contracts, but the apex is dyskinetic (arrows). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

- A. LV aneurysm
- B. LV pseudoaneurysm
- C. Apical ballooning syndrome
- D. LV noncompaction
- E. Dilated cardiomyopathy

15-10. A 55-year-old woman with a prior history of a modified radical mastectomy for a left breast adenocarcinoma was admitted to the emergency department complaining of acute dyspnea. Chest radiography showed cardiomegaly and left pleural effusion. An echo was performed, and the apical four-chamber view is illustrated in [Figure 15-8](#). With regard to cardiac tamponade, which of the following statements is *false*?

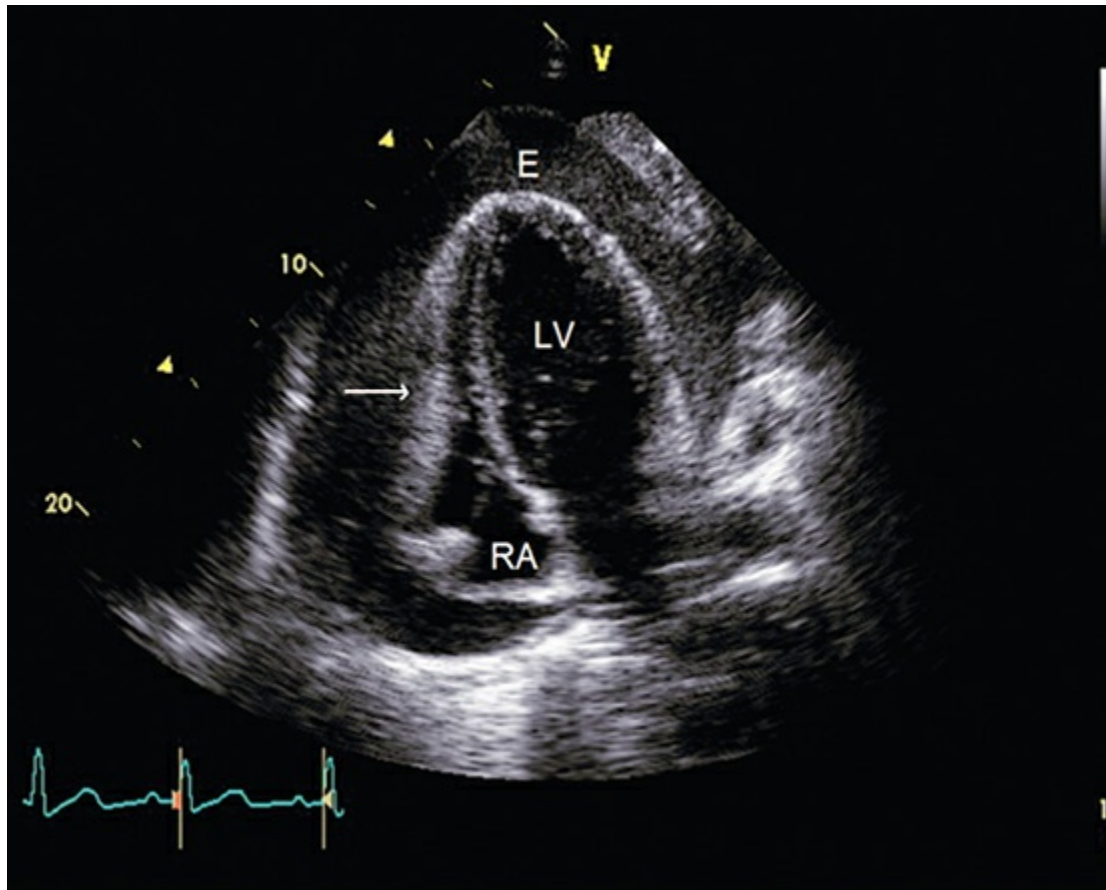


FIGURE 15-8 Right ventricular compression (arrow) in cardiac tamponade (apical four-chamber plane).

- A. Right atrium (RA) collapse during atrial systole is the most specific sign of tamponade
- B. Diastolic collapse of the right ventricular (RV) free wall is the most sensitive sign of tamponade
- C. Left ventricular outflow tract obstruction (LVOT) velocities increase significantly with inspiration
- D. Transmitral diastolic gradient during inspiration increases significantly
- E. All of the above

ANSWERS

15-1. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 15*) Short wavelengths yield excellent resolution in echo imaging (option A) because the shorter the cycle length, the smaller the object that will reflect the signal and be detected by the echo scanner. Because wavelength is inversely related to frequency, transducers that emit a high-frequency signal (≥ 3.5 – 7.0 MHz) yield high-resolution images (option B). Because ultrasonic beams diverge as they propagate away from the transducer, the width of the beam can become sufficiently great to encompass multiple targets and decrease resolution (option D). The degree of beam divergence is also less with high-frequency sonic energy than with low-frequency signals.

15-2. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 15*) The abnormal mitral inflow patterns are often useful in suggesting the presence and severity of diastolic dysfunction. Several variables other than diastolic function, however, are capable of influencing transmitral filling velocities. Transmitral Doppler filling dynamics are affected by the age of the patient (option A), concomitant mitral regurgitation, high-flow states, changes in heart rate (option B),¹ respiration (option C), and the position of the Doppler sample volume within the mitral valve orifice (option D).²

15-3. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 15*) Transmitral flow demonstrates a restrictive pattern, with

an abnormally high E/A ratio and a markedly shortened E wave deceleration time (see [Figure 15-1a](#)). Concomitant pulmonary venous tracings show a very low S velocity and elevated D velocity ($S \ll D$) (see [Figure 15-1b](#)) and a prolonged atrial reversal wave, thus predicting elevated left atrial pressure.³ In severe LV diastolic dysfunction, tissue Doppler imaging (TDI) of the mitral annulus should show marked blunting of both Em and Am velocities. An exception to this occurs in constrictive pericarditis, where Em is relatively normal at the medial mitral annulus and only mildly reduced at the lateral mitral annulus. Thus when transmitral and pulmonary venous Doppler suggest severe diastolic dysfunction, this TDI pattern suggests constrictive rather than restrictive physiology (amyloid-induced cardiomyopathy [CM], hypereosinophilic CM, endomyocardial fibrosis, and idiopathic restrictive CM).

- 15-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 15*) A number of technical factors can influence jet size, including instrument gain, the angle of incidence of the interrogating beam, the frequency and pulse repetition rate of the transducer, and the temporal sampling rate.⁴ Therefore, measurements derived from the size of the turbulent jet recorded by color Doppler are at best semiquantitative and should not be expected to correlate with the volume of blood contained in the flow disturbance.
- 15-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 15*) Echocardiography is routinely used to assess aortic pathology in patients with Marfan syndrome. The aortic pathology is characterized by symmetrical dilatation of the annulus, sinuses of Valsalva, and aorta ([Figure 15-3](#)). Aortic leaflet coaptation may be compromised, leading to AR. In sinus of Valsalva aneurysm, the lesion causes asymmetric dilatation of the aorta. Supravalvular aortic stenosis is recognized as an hourglass narrowing or a discrete fibrous ridge just superior to the aortic valve leaflets, whereas coarctation of the aorta presents a more localized, abrupt luminal reduction in the descending aorta or distal portion of the aortic arch; both of these conditions tend to cause more of a systolic than a diastolic murmur.
- 15-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 15*) Several potential sources of error exist in the estimation of the transvalvular aortic gradient by CW Doppler recordings. It is imperative that Doppler signals from the stenotic jet be obtained with an angle of incidence of less than 20 degrees so as not to underestimate the velocity or gradient. For this purpose, and because two-dimensional techniques rarely reveal the precise direction of the jet, each Doppler examination must use all possible windows and angulations, and the window that provides the highest velocity is chosen. Also, one must be careful to account for the proximal flow velocity in the Bernoulli equation if it is 1.5 m/s or greater. In the adult, CW Doppler can occasionally overestimate peak systolic pressure gradients, especially in patients with narrow ascending aortas (due to pressure recovery). Lastly, in patients with concomitant dynamic LV outflow obstruction, it is usually difficult to separate the increased velocity caused by each of these conditions.
- 15-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 15*) Perhaps the most important contribution of echocardiographic imaging to the assessment of AR is in identifying its etiology and adaptation of the LV to the volume overload. Aggressive vegetations can cause perforation or distortion of the affected leaflet, leading to varying degrees of valvular regurgitation. AR caused by infectious endocarditis can be identified by the presence of valvular vegetations ([Figure 15-5](#)), whereas functional AR caused by diseases of the aorta can be identified by anatomic changes of the aortic root or dissection.
- 15-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 15*) SAM is not pathognomonic for HCM, and it can occur in other conditions involving hyperdynamic LV function (eg, hypovolemia/dehydration, anemia) or anterior displacement of the annulus (eg, use of a rigid mitral ring in mitral valve repair).
- 15-9. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 15*) Echocardiography is of great value in assessing complications associated with acute myocardial infarction (AMI).⁵ Postinfarction LV aneurysms are recognized as wide-mouthed, thin-walled myocardial segments that display dyskinetic expansion during systole (option A). Pseudoaneurysms (most often secondary to a free wall rupture, which is subsequently sealed off by clot and pericardial inflammation) is distinguished from a true aneurysm by the presence of a narrow neck, multilayered thrombi, and characteristic Doppler flow signals at the junction with the ventricle.⁶ Because the risk of rupture is high, accurate diagnosis and prompt surgical repair of pseudoaneurysms is important (option B). Takotsubo cardiomyopathy (also called stress cardiomyopathy or apical ballooning syndrome) is a syndrome of sudden-onset chest pain associated with significant LV dysfunction but no occlusive coronary disease and only minor troponin elevations.⁷ Echocardiography is well suited for evaluation in this setting and often shows dramatic apical ballooning with preservation (or hyperkinesis) of the LV basal segments (option C). LV noncompaction is a form of cardiomyopathy that is characterized by a prominent noncompacted layer of myocardium lining the cavity of the left ventricle.⁸ A ratio of > 2.0 between the systolic thicknesses of the noncompacted and compacted myocardial layers is suggestive of noncompaction (option D).⁹ The echocardiographic findings in dilated cardiomyopathy include an increased LV end-diastolic diameter and decreased ejection fraction, in the absence of other features specifically associated with other etiologies (option E).
- 15-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 15*) Because diastolic pressures are slightly lower in the right heart than in the left, the RA and RV are usually the first chambers to exhibit evidence of increased intrapericardial pressure. High intrapericardial pressure can cause compression or collapse of right heart chambers. Invagination of the RA wall during atrial systole is a sensitive (but not specific) sign of tamponade. Diastolic collapse or buckling of the RV free wall is a more specific sign of tamponade. Doppler echocardiographic recordings in patients with tamponade demonstrate an exaggeration of the normal respiratory variation in ventricular inflow and outflow. Thus transmitral and

LVOT velocities decrease significantly with inspiration, most likely because of enhanced ventricular interdependence and a marked decrease in the transmitral diastolic gradient during inspiration. The latter is caused both by high intrapericardial pressure and by leftward motion of the interventricular septum from increased RV filling.

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CHAPTER 16

Magnetic Resonance Imaging of the Heart

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 16-1.** Tissue characterization with mapping or weighted imaging using assessments of T1, T2, or T2* relaxation is increasingly used in cardiovascular magnetic resonance (CMR).^{1,2} Which of the following conditions *cannot* be identified by T2 or T2*-weighted imaging?
- A. Myocardial edema in the setting of acute myocardial infarction (MI)
 - B. Myocardial edema in the setting of myocarditis
 - C. Myocardial hemorrhage
 - D. Iron-overload cardiomyopathy
 - E. None of the above
- 16-2.** Although a relatively safe imaging modality, CMR does have the potential for serious and even lethal events. Which of the following statements regarding the safety of common metallic implants and electronic devices commonly found in cardiac patients is *false*?
- A. Current coronary stents are safe and can be imaged immediately after implantation
 - B. Current prosthetic valves are safe and can be imaged immediately after implantation
 - C. Weakly ferromagnetic implants are safe and can be imaged immediately after implantation
 - D. Swan-Ganz catheters contain metal and are considered unsafe
 - E. Transdermal patches may need to be removed before the procedure
- 16-3.** CMR is unique in that, with a single imaging modality, one can identify abnormalities of myocardial perfusion or wall motion with a relatively high spatial resolution and without ionizing radiation. Based on multimodality appropriate use criteria, in which of the following patients is stress CMR considered appropriate?
- A. Patients presenting with chest pain at a high pretest probability of coronary artery disease (CAD)
 - B. Patients at an intermediate pretest probability of CAD with an uninterpretable ECG
 - C. Patients with an abnormal or uncertain exercise ECG
 - D. Patients with obstructive CAD of uncertain significance
 - E. All of the above
- 16-4.** A 54-year-old obese woman was admitted to the emergency department complaining of worsening chest discomfort. After being diagnosed with an acute myocardial infarction, she underwent successful stenting of the left anterior descending artery. An echocardiogram was ordered to assess left ventricular function, but the image quality was suboptimal due to poor acoustic windows. A cardiac magnetic resonance exam was then ordered to provide an assessment of:
- A. Myocardial salvage
 - B. Microvascular obstruction
 - C. The extent of late gadolinium enhancement (LGE) as a predictor of survival and adverse cardiac events
 - D. The presence of T2 hyperintensity in the affected territory as an indicator of infarct acuity
 - E. All of the above
- 16-5.** A 65-year-old man with a 20-year history of poorly controlled diabetes presented to the emergency department complaining of acute dyspnea. After the initial tests, the diagnosis of acute decompensated heart failure (HF) was confirmed. In order to establish the underlying etiology and, importantly, to exclude chronic ischemic heart disease as a potentially reversible cause, a CMR was performed. An LGE image in a two-chamber long-axis orientation is illustrated in [Figure 16-1](#). Which of the following statements regarding LGE is *false*?



FIGURE 16-1 Late gadolinium-enhanced inversion recovery gradient echo image in a two-chamber long-axis orientation in a patient with systolic heart failure. Two areas of prior myocardial infarction are seen: a subendocardial infarct in the basal to midinferior wall and a small apical infarct with an associated apical thrombus.

- A. The absence of LGE rules out the diagnosis of underlying CAD
- B. Patients without obstructive CAD may have evidence of LGE
- C. The presence and amount of LGE is prognostically important in the setting of CAD
- D. CMR is considered an appropriate technique for the evaluation of patients with new-onset HF
- E. Patients with nonischemic causes of HF may or may not have evidence of LGE

16-6. A 35-year-old man with no prior cardiac history was admitted to the emergency department with chest pain, troponin elevation, and no evidence of angiographically detectable stenoses within the epicardial coronary arteries. The patient underwent CMR, and an LGE image in a basal short-axis orientation is shown in [Figure 16-2](#). Which of the following is the most likely diagnosis?

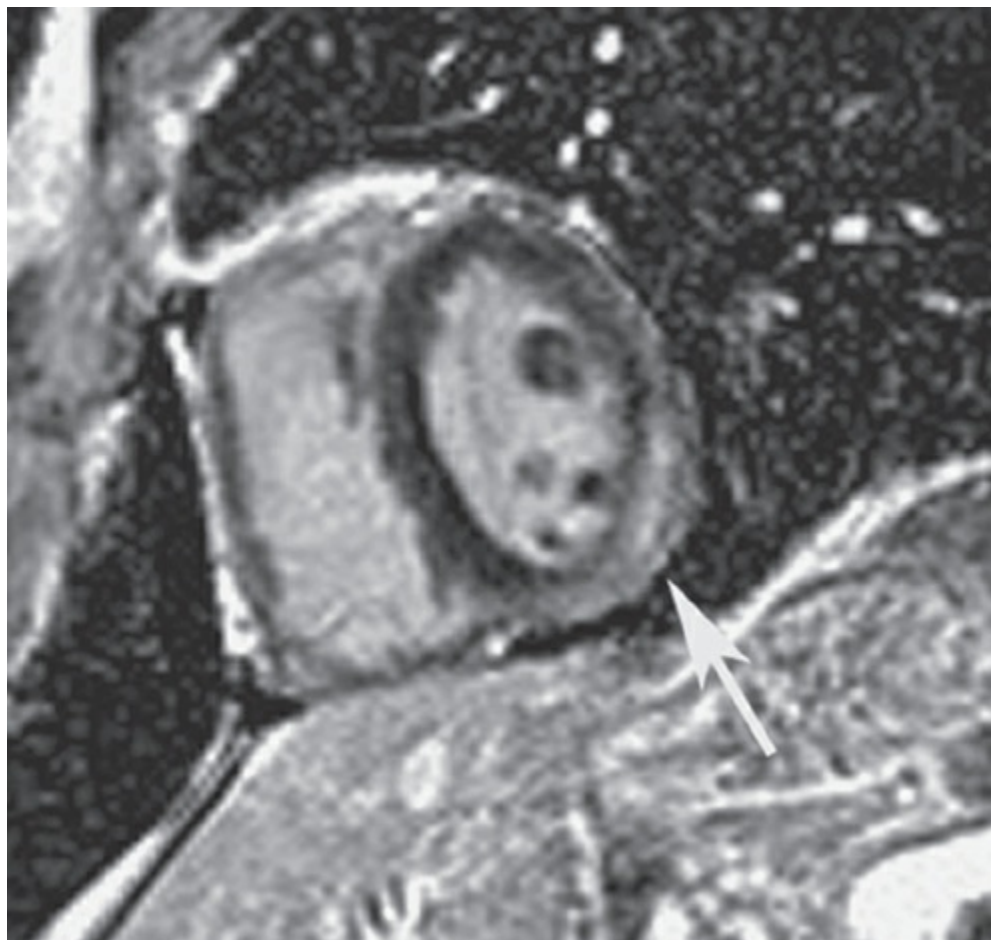


FIGURE 16-2 Late gadolinium-enhanced (LGE) inversion recovery gradient echo image in a basal short-axis orientation. LGE is noted in the midwall and subepicardium in the inferolateral wall (arrow).

- A. Noncardiac chest pain

- B. Hypertrophic cardiomyopathy (HCM)
- C. Acute myocardial infarction
- D. Viral myocarditis
- E. Takotsubo or stress cardiomyopathy

16-7. A 57-year-old woman with no prior cardiac history was admitted to the emergency department complaining of a 6-month history of dyspnea. On physical examination, she had jugular venous distension, hepatomegaly, tense ascites, severe bilateral lower limb edema, and an S3 gallop. After an initial management she underwent CMR, and a four-chamber T1-weighted image as well as diastolic short-axis images from a real-time cine acquisition during free breathing are illustrated in [Figure 16-3](#). Which of the following statements regarding the diagnosis is *false*?

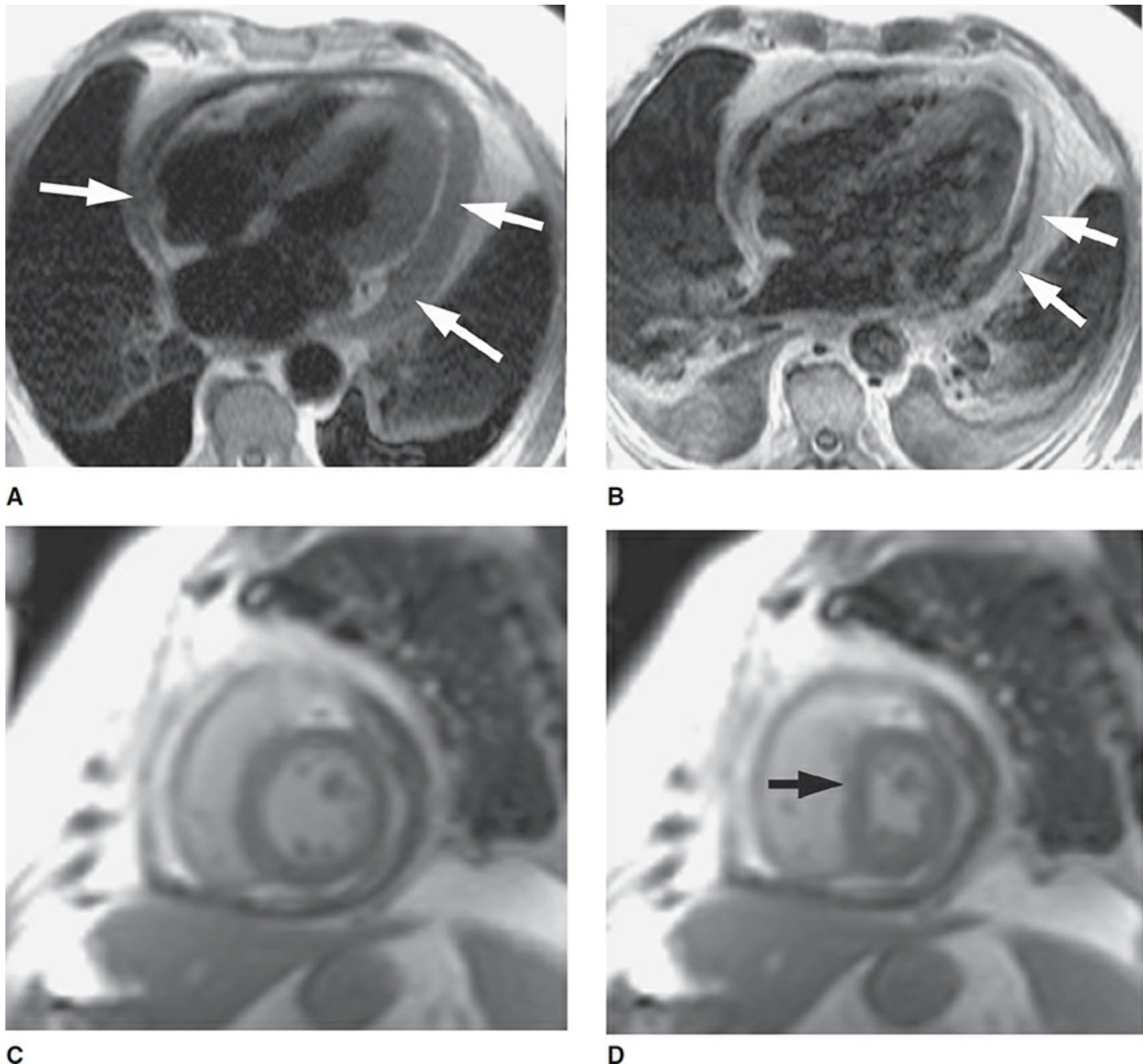


FIGURE 16-3 (A) Four-chamber T1-weighted spin echo demonstrating markedly increased pericardium (dark band, arrows). (B) Same image acquired after contrast showing pericardial enhancement (arrows). (C) and (D) Expiratory and inspiratory, respectively—diastolic short-axis frames from a real-time cine acquisition during free breathing. Note the marked septal flattening during inspiration (arrow) consistent with increased ventricular interdependence.

- A. Pericardial thickness of 4 mm or more is considered abnormal
- B. Pericardial thickness may not be accurately quantified in the presence of an effusion
- C. This disease can occur with normal pericardial thickness
- D. The presence of extensive pericardial LGE may identify a subgroup of patients in whom the disease can revert with anti-inflammatory therapy
- E. Pericardial LGE is synonymous with pericardial fibrosis

16-8. An 85-year-old woman with no prior cardiac history presented to the emergency department complaining of dizziness. The patient denied any other associated symptoms, and initial test results were within normal range. As part of the dizziness workup, a transthoracic echocardiogram was performed, which showed a large interatrial mass. For further characterization of the mass, the patient underwent CMR, and a T1-weighted image before and after the application of a fat suppression pulse is illustrated in [Figure 16-4](#). Which of the following conditions is the most likely diagnosis?

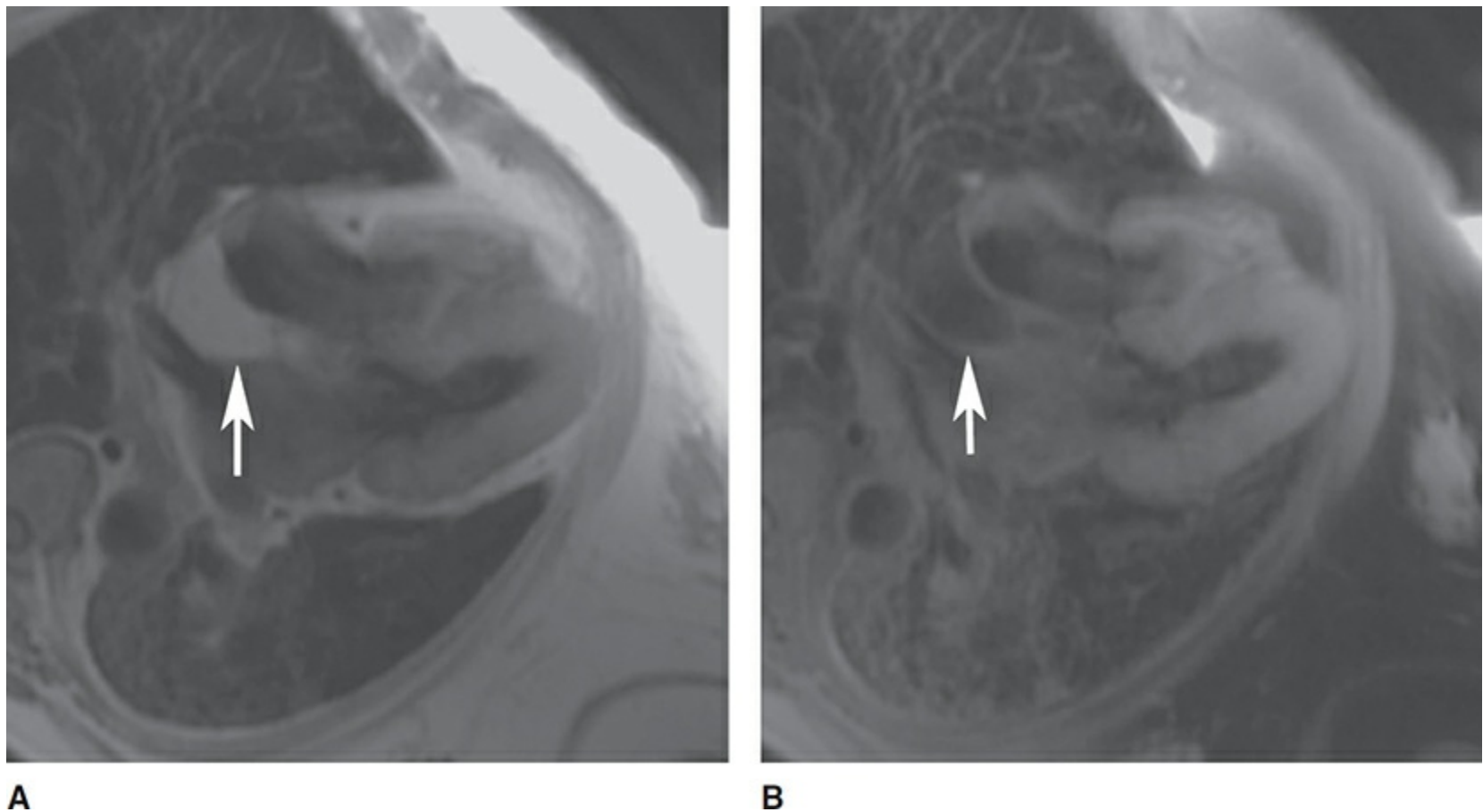


FIGURE 16-4 On standard T1-weighted spin echo images, the lesion is hyperintense (A; arrow). After the application of a fat suppression pulse, the signal from the lesion is nulled (B; arrow).

- A. Lymphoma
- B. Rhabdomyosarcoma
- C. Angiosarcoma
- D. Lipoma
- E. Myxosarcoma

16-9. A 75-year-old man with a prior history of dyslipidemia, hypertension, and poorly controlled diabetes was referred to cardiology for a CMR exam, three days after his admission to the emergency department for retrosternal chest discomfort. A four-chamber long-axis orientation with different inversion times (TI) is illustrated in [Figure 16-5](#). Which of the following feature does *not* support the diagnosis of a thrombus?

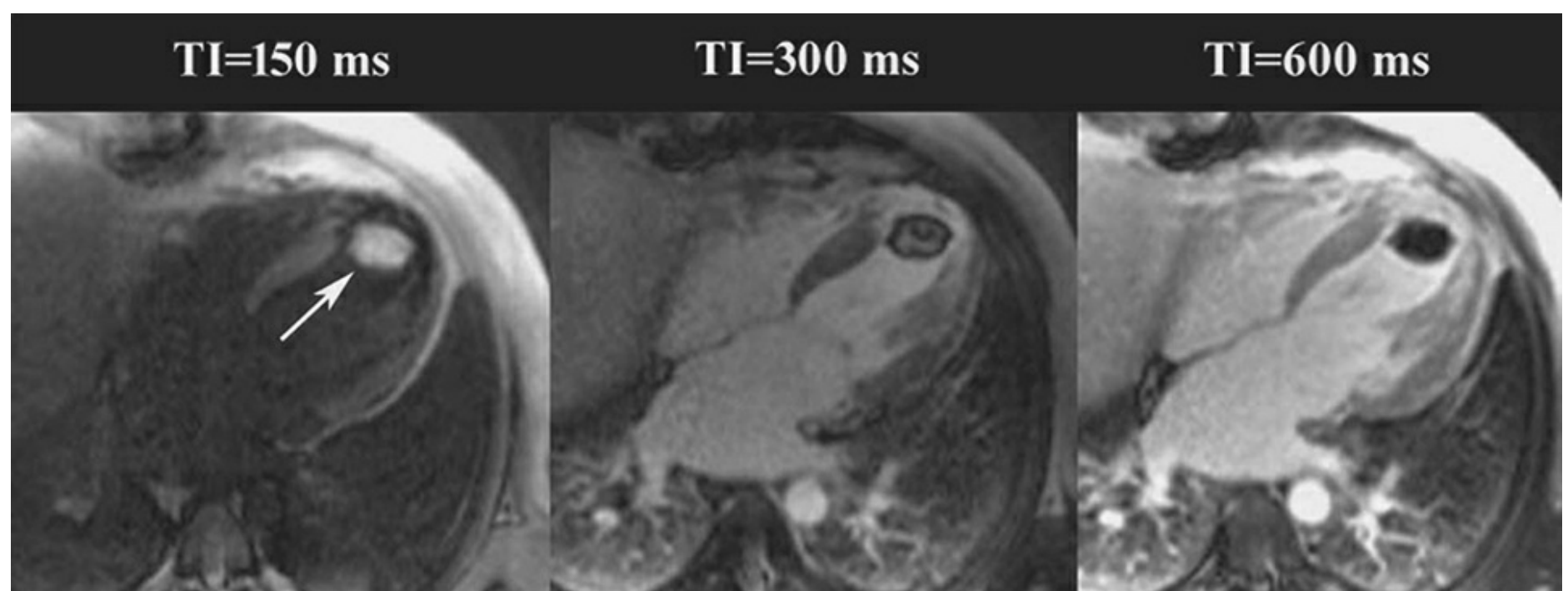


FIGURE 16-5 Four-chamber long-axis orientation with different inversion times (TI).

- A. Homogenous appearance
- B. Lack of mobility
- C. Hyper- or iso-intense with short inversion time (TI) and hypointense with long TI
- D. Location in the LV adjacent to areas of scar
- E. None of the above

16-10. Although LGE techniques are widely used for identifying myocardial scar and thus inferring viability, dobutamine stress CMR is also used to measure LV myocardial contractile reserve and thus to identify myocardial segments that have the potential to recover systolic function after successful epicardial coronary arterial revascularization. Which of the following is *not* an advantage of using dobutamine stress CMR for assessing myocardial viability?

- A. It can be administered to patients with reactive airways disease

- B. It can be administered to patients with severe renal dysfunction
- C. The prediction of improvements in regional wall motion or radial thickening is incremental above and beyond LGE
- D. None of the above
- E. All of the above

ANSWERS

- 16-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 16*) High signal on T2-weighted imaging can demonstrate myocardial edema, such as in the setting of acute MI or myocarditis. T2*-weighted imaging is sensitive to iron in the heart and can identify iron overload cardiomyopathy and myocardial hemorrhage in the setting of acute MI.
- 16-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 16*) All current coronary stents and prosthetic valves are safe and can be imaged immediately after implantation. Many other cardiac or vascular implants are nonferromagnetic and can also be scanned at any time, or they are weakly ferromagnetic and a delay of 6 weeks before MRI is recommended to allow for endothelialization. Swan-Ganz catheters contain metal and are considered unsafe. Similarly, some medication patches (including transdermal patches) contain metallic foil and may need to be removed before the procedure.
- 16-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 16*) Based on multimodality appropriate use criteria, stress CMR is considered appropriate for patients at a high pretest probability of CAD or an intermediate pretest probability of CAD with an uninterpretable ECG or inability to exercise.³ It is also appropriate for patients with an abnormal ECG who are intermediate to high risk as well as those with an abnormal or uncertain exercise ECG or those with obstructive CAD of uncertain significance noted on computed tomography (CT) or invasive coronary angiography.
- 16-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 16*) Today, perhaps the most widely used imaging method for identifying myocardial injury and fibrosis associated with myocardial infarction is through CMR-based assessments of LGE.⁴ LGE has several important uses in the setting of patients with suspected CAD. These include identification of the extent of acute and remote MI, the prediction of recovery of myocardial contractility after successful coronary artery revascularization, characterization of prognosis, visualization of cardiac thrombus or microvascular obstruction and, when combined with T2 imaging methods, localization of the area of myocardial salvage and infarct acuity.
- 16-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 16*) The first step in the evaluation of the patient with new-onset HF is to establish the underlying etiology and, importantly, to exclude ischemic heart disease as a potentially reversible cause. CMR is considered an appropriate technique for the evaluation of patients with new-onset HF.⁵ The presence of LGE in a coronary distribution can support the diagnosis of underlying CAD, but its absence does not rule it out because patients with extensive hibernating myocardium may not have LGE.⁶ Patients with HF without obstructive CAD may not have evidence of LGE,⁷ or they may have evidence of LGE, usually in a noninfarct pattern, but occasionally in an infarct pattern because of transient thrombotic occlusion of a nonobstructive artery, embolization, or spontaneous coronary dissection. The presence and amount of LGE are prognostically important.
- 16-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 16*) The pattern of LGE can be quite useful in differentiating causes of cardiomyopathies.⁸ The finding of LGE in the midwall and subepicardium of the LV is seen in viral myocarditis and has been validated against histopathology.⁸ The finding of “patchy” LGE in myocardial segments with marked hypertrophy, or in the septal insertion points, is suggestive of HCM. The finding of LGE in the subendocardium of the LV following a distinct coronary territory is characteristic of myocardial infarction. Takotsubo or stress cardiomyopathy is a clinical syndrome characterized by chest pain and ECG changes that mimic an acute myocardial infarction, in which there is generally no LGE.
- 16-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 16*) The hallmarks of constrictive pericarditis are increased pericardial thickness, pericardial inflammation, and ventricular interdependence. The pericardium can be visualized and measured in a number of sequences, although T1-weighted black-blood imaging is usually the standard,⁹ where the pericardium appears as a hypointense linear structure surrounded by hyperintense fat layers (*Figure 16-3A*). Although normal pericardial thickness is less than 1 mm, on CMR, 1 to 3 mm is considered normal because of limitations in spatial resolution,⁹ and a thickness of 4 mm or more is considered abnormal. Pericardial thickening may be focal or diffuse. It is important to realize that pericardial thickness may not be accurately quantified in the presence of an effusion (both are hypointense on black-blood imaging), that constriction can occur with normal pericardial thickness, and that increased thickness is not synonymous with constriction. The presence of extensive LGE, which may represent dense inflammation, identifies a subgroup of patients in whom constrictive pericarditis can revert with anti-inflammatory therapy.^{10,11}
- 16-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 16*) High signal intensity on T1-weighted images, besides the presence of recent hemorrhage, can also be caused by fat. Together with signal reduction with fat suppression

techniques, hyperintensity on T2-weighted imaging, a lack of first-pass perfusion, and an absence of LGE, CMR allows for the straightforward diagnosis of lipoma. Although less accurate, CMR can also help differentiate benign from malignant neoplasms (lymphoma, rhabdomyosarcomas, angiosarcomas, and myxosarcomas). Larger sizes, invasion of adjacent structure(s), the presence of pleural or pericardial effusions, prominent first-pass perfusion, or positive LGE are all features seen more commonly in malignancy.^{12,13}

- 16-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 16*) The main strength of CMR in the evaluation of cardiac masses is probably the ability to differentiate between cardiac thrombi from tumors. Features supporting the diagnosis of thrombus include location in the LV adjacent to areas of scar or the left atrial appendage, homogenous appearance, lack of mobility, isointensity or hypointensity on T2-weighted imaging, and absence of perfusion or LGE. A thrombus is hyper- or iso-intense with short TI and hypointense with long TI.
- 16-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 16*) A particular advantage of low-dose dobutamine infusions for assessing myocardial viability is that they can be administered to patients with reactive airways disease as well as to those with renal dysfunction in whom the use of gadolinium may be contraindicated. In addition, there is some evidence that low-dose dobutamine stress CMR assessments of improvements in regional wall motion or radial thickening are complementary and may even be superior to the assessments of LGE, particularly in those individuals who have an intermediate nontransmural extent of LGE.¹⁴

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Computed Tomography of the Heart

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 17-1.** Advancements in CT technology have made it possible to noninvasively image the beating heart. Which of the following statements regarding cardiac CT is *false*?
- A. Cardiac CT can assess left and right ventricular remodeling
 - B. Cardiac CT can assess regional myocardial wall motion and thickening
 - C. Cardiac CT is comparable to first-pass radionuclide angiography for the calculation of post-MI LVEF
 - D. Cardiac CT can detect myocardial iron overload
 - E. Cardiac CT can detect intracardiac thrombus
- 17-2.** A 35-year-old obese woman with a significant family history of premature coronary heart disease presented to the emergency department complaining of a 2-week history of intermittent chest pain. Initial ECG and biomarkers were within normal limits. After an equivocal stress test, she underwent cardiac CT. Which of the following statements about cardiac CT and coronary artery calcification (CAC) is *false*?
- A. The severity of angiographic coronary artery stenosis is directly related to the total CAC
 - B. Cardiac CT can detect coronary atherosclerosis at its earliest stages
 - C. CAC is caused by atherosclerosis in the coronary arteries
 - D. CAC is not found in normal coronary arteries
 - E. There is a strong linear correlation between total coronary artery plaque area and the extent of CAC
- 17-3.** A 55-year-old woman with a prior history of poorly controlled diabetes, hypertension, and dyslipidemia presented to the emergency department complaining of a retrosternal chest pain radiating to her left arm. In the absence of new ECG changes or cardiac biomarker elevation, she underwent cardiac CT. This patient was scanned with a dual-source CT, and the heart rate during the time of the scan was 105 beats/min. The rendered three-dimensional (3D) image of the heart as well as the maximum-intensity projection (MIP) image of the same patient are illustrated in [Figure 17-1](#). Which of the following would *not* be useful for decreasing motion-related artifacts?

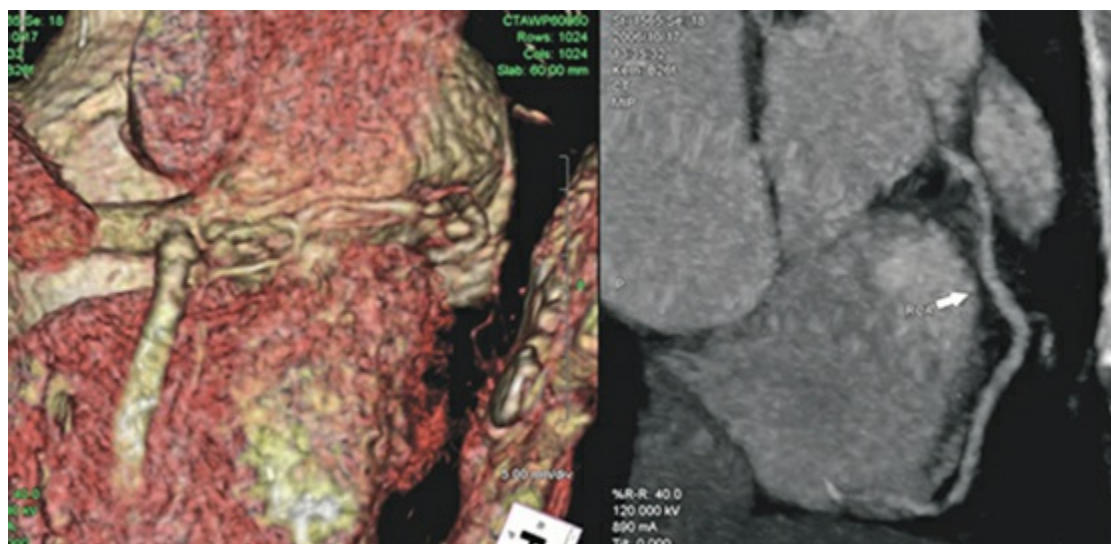


FIGURE 17-1 Left panel: Three-dimensional (3D) rendering image of a heart with significant motion artifact affecting the interpretation of the distal right coronary artery (RCA). Right panel: Maximum-intensity projection (MIP) image of the same patient showing significant transitional motion artifact in the proximal and mid RCA.

- A. Image acquisition of less than 50 milliseconds
- B. Use of oral and/or intravenous β -blockers prior to scanning
- C. Use of sublingual tablets or spray of nitroglycerin
- D. Breath-hold strategy during scanning

E. None of the above

17-4. A 64-year-old man with suspected acute coronary syndrome (ACS) was referred to cardiology for coronary CT angiography (CCTA). Which of the following statements about the diagnostic performance of the CCTA is *false*?

- A. The diagnostic accuracy for ACS with CCTA is lower than stress echocardiography.
- B. The diagnostic accuracy for ACS with CCTA is higher than stress nuclear imaging.
- C. The high negative predictive value of CCTA is a valuable tool in the exclusion of obstructive CAD
- D. CCTA is useful in the risk stratification of symptomatic CAD
- E. CCTA is an accurate tool in the assessment of chest pain in patients with intermediate risk of CAD

17-5. A 78-year-old woman with multivessel coronary artery disease and prior PCI to the left anterior descending coronary artery (LAD) was referred to cardiology for coronary stent evaluation following an episode of severe central chest pain. A CCTA was performed, and it is shown in [Figure 17-2](#). Which of the following factors can potentially *reduce* the diagnostic accuracy of CCTA for the noninvasive evaluation of in-stent restenosis?



FIGURE 17-2 Evaluation of coronary stents. Occluded stent in the proximal left anterior descending (coronary artery).

- A. Imaging artifacts
- B. Stent location
- C. Heart rate
- D. Stent diameter
- E. All of the above

17-6. A 37-year-old woman with no prior cardiac history was admitted to the emergency department complaining of atypical chest pain. After the initial ECG and biomarkers were within normal limits, she underwent coronary computed tomography angiography to exclude coronary artery disease. CCTA is illustrated in [Figure 17-3](#). Which of the following statements about congenital anomalies of the coronary arteries is *false*?

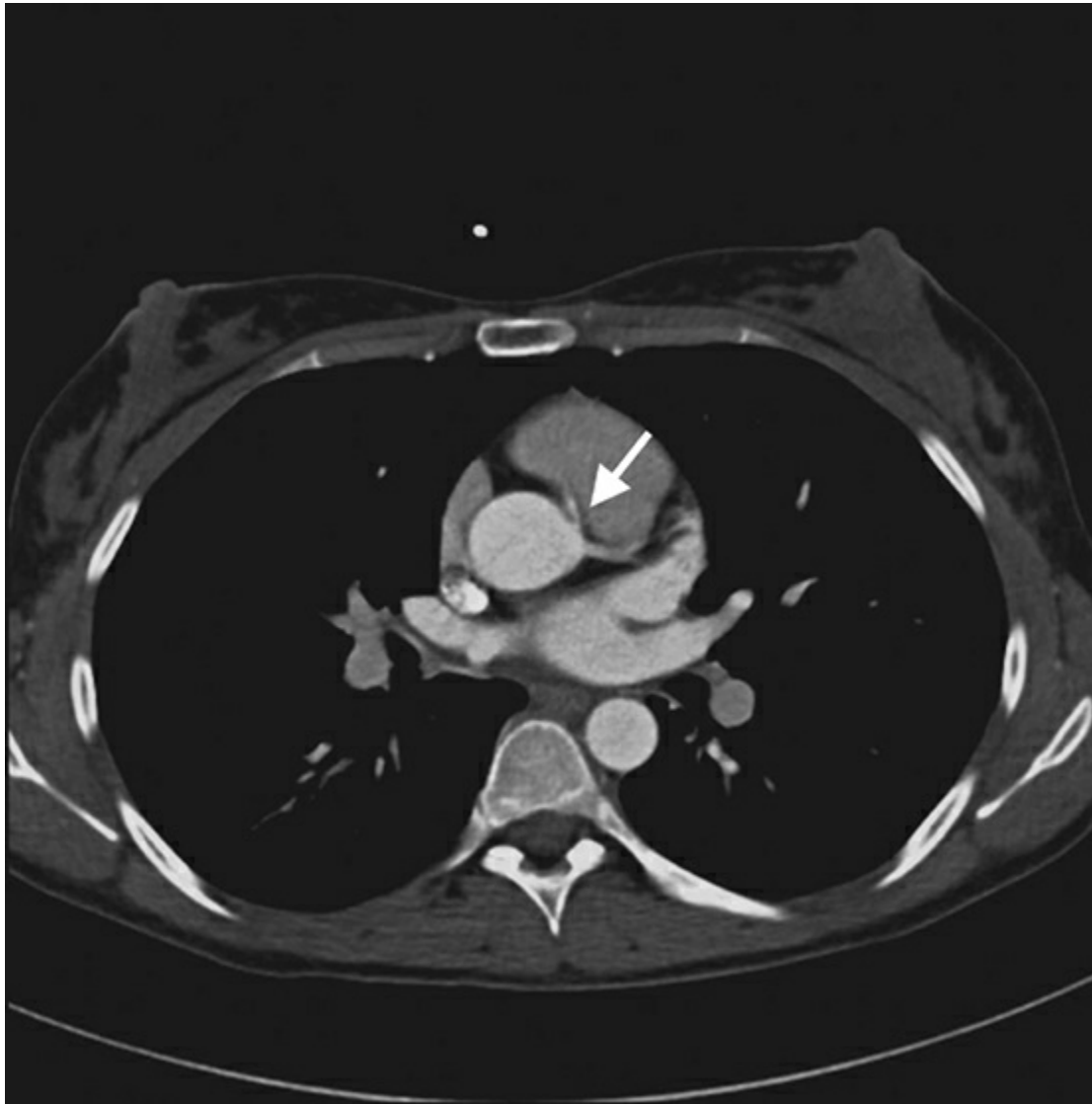


FIGURE 17-3 Anomalous right coronary artery. Note the right coronary artery (arrowhead) arising to the left of midline from the left sinus of Valsalva taking interarterial course.

- A. Congenital anomalies of the coronary arteries are reported in 0.3% to 1% of the general population
- B. Approximately 20% of coronary anomalies can be hemodynamically significant
- C. An interarterial course is the coronary anomaly most commonly associated with sudden cardiac death
- D. None of the above
- E. All of the above

17-7. An 85-year-old woman with a prior history of poorly controlled type 2 diabetes, hypertension, dyslipidemia, rheumatoid arthritis, and multivessel coronary heart disease was admitted to the emergency department with severe symptomatic aortic stenosis. She underwent a contrast-enhanced CTA in advance of the transcatheter aortic valve replacement (TAVR). The left main coronary artery craniocaudal height is illustrated in [Figure 17-4](#). Which of the following factors is predictive of an increased risk of coronary occlusion during TAVR?

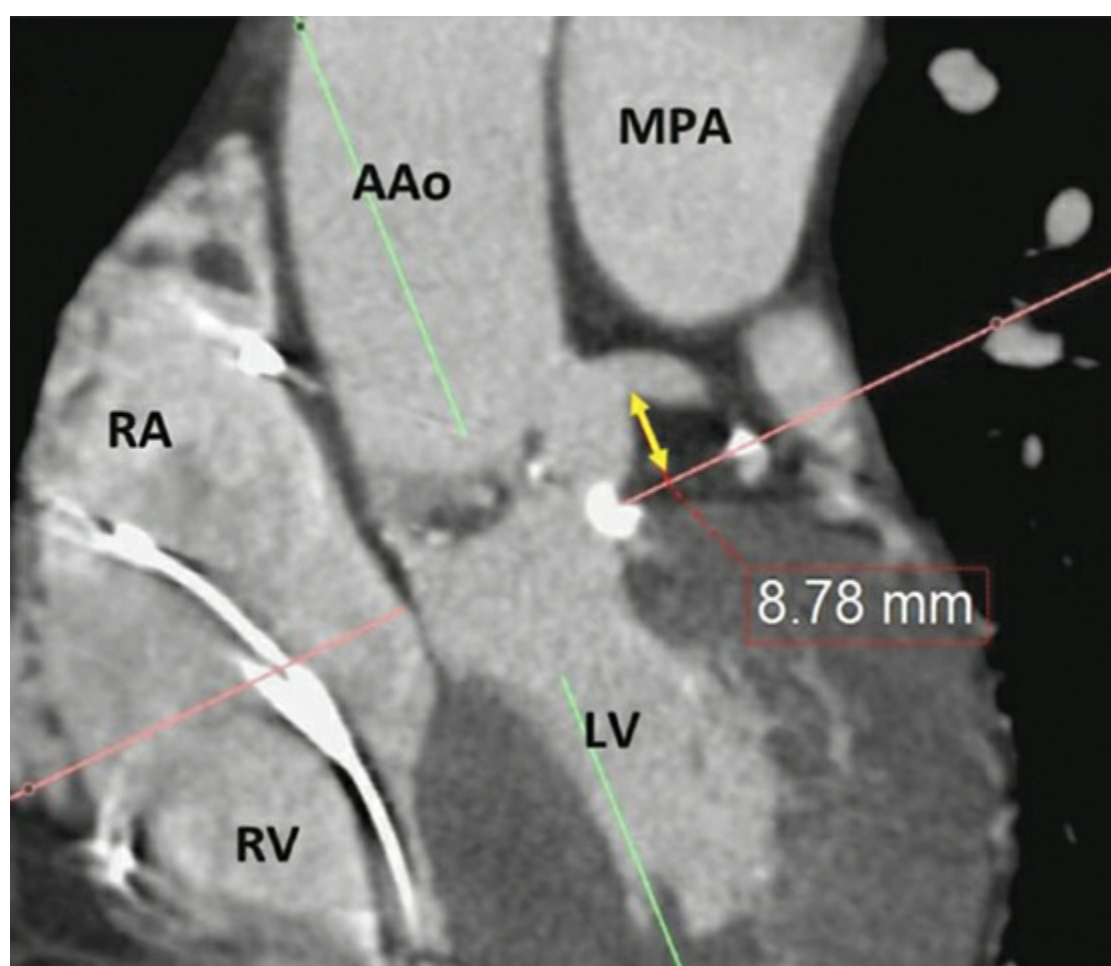


FIGURE 17-4 Left main coronary artery craniocaudal height measured perpendicular to the annular plane. The left main

coronary artery height is 8.78 mm. AAo, ascending aorta; LV, left ventricle; MPA, main pulmonary artery; RA; right atrium; RV, right ventricle.

- A. Left main height of lesser than 12 mm
- B. A shallow of Valsalva mean diameter (cusp to commissures) of < 30 mm
- C. A sinus of Valsalva-to-annular ratio of less than 1.25
- D. None of the above
- E. All of the above

17-8. The main historical limitation of cardiac CT has been radiation exposure, which was previously reported to be two to four times the radiation dose of diagnostic invasive coronary angiography. Which of the following strategies has been shown to provide the greatest reduction in radiation dose during CCTA?

- A. Using prospective ECG-gated or sequential CCTA image acquisition
- B. Decreasing the tube voltage in nonobese patients
- C. Adopting iterative reconstruction algorithms to allow for significant noise reduction
- D. Using scan acquisition modes employing fast helical pitch technique
- E. None of the above

17-9. A 75-year-old man with a prior history of dyslipidemia, hypertension, poorly controlled diabetes, multivessel CAD, and multivessel PCI was referred to cardiology for CCTA 3 days after his admission to the emergency department for retrosternal chest discomfort. A CCTA view of the 3 major epicardial vessels is illustrated in [Figure 17-5](#). Which of the following statements regarding the prognostic value of CCTA is *false*?

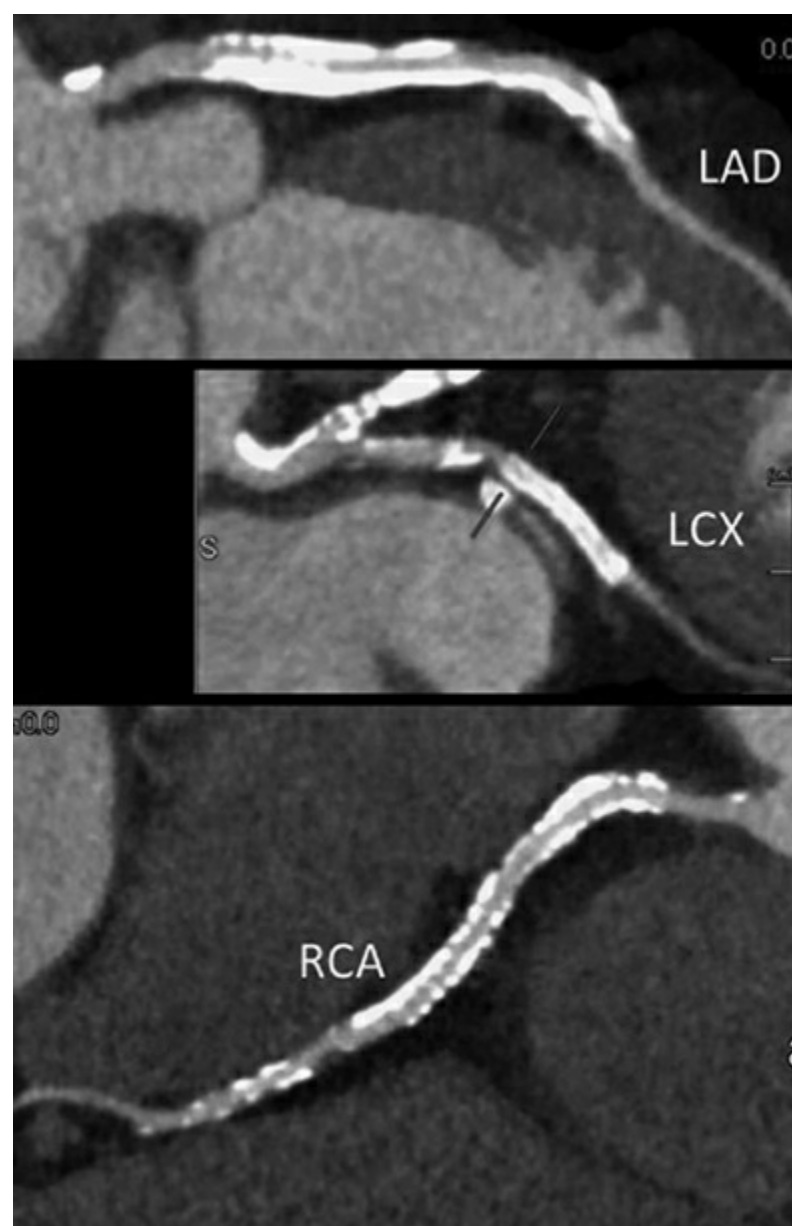


FIGURE 17-5 Conventional cardiac computed tomography angiography (CCTA) for evaluation of all three coronary artery vessels. LAD, left anterior descending (artery); LCX, left circumflex artery; and RCA, right coronary artery.

- A. The presence of any stenosis greater than 50% predicts an increased risk of cardiovascular events
- B. CCTA is useful for establishing the diagnosis, but not the true extent, of CAD
- C. Plaque morphology by CT confers incremental prognostic information beyond that provided by percent stenosis alone
- D. CCTA measures of CAD severity and LVEF have independent prognostic value
- E. None of the above

17-10. In patients undergoing repeat coronary artery bypass surgery (CABG), CTA scanning has several advantages. Which of the following does *not* support the use of CTA as a primary noninvasive imaging tool for the evaluation of patients prior to CABG?

- A. CTA may guide the surgical approach by defining the position of the sternum relative to the underlying right ventricle

- and internal mammary artery bypass graft
- B. CTA can assess the diameter and calcification of the aorta
- C. CTA can assess the presence of coronary stenoses within the bypass graft
- D. CTA can assess the presence of coronary stenoses within the native coronary arteries and anastomotic sites
- E. None of the above

ANSWERS

- 17-1. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 17*) While cardiac CT can provide some information about tissue characterization, it cannot reliably detect iron overload, and this is typically assessed by cardiac MR. Cardiac CT can assess left and right heart size as well as regional myocardial wall motion and thickening (options A and B).^{1,2} Cardiac CT is comparable to first-pass radionuclide angiography for the calculation of left ventricular ejection fraction in patients with myocardial infarction (option C).³ Cardiac CT could effectively detect intracardiac masses such as thrombi and tumors, particularly when these masses are nonmobile or calcified (option E).⁴
- 17-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 17*) The presence of CAC is clearly indicative of coronary atherosclerosis,^{5,6} serving as a marker for CAD; but importantly, the severity of angiographic coronary artery stenosis is not directly related to the total CAC. CAC is thought to begin early in life, and CT can detect coronary atherosclerosis at its earliest stages. Although lack of calcification does not categorically exclude the presence of atherosclerotic plaque, calcification occurs exclusively in atherosclerotic arteries and is not found in normal coronary arteries. A strong linear correlation exists between total coronary artery plaque area and the extent of CAC.
- 17-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 17*) The coronary arteries move independently throughout the cardiac cycle, and even at relatively slower heart rates (< 70 beats/min), they exhibit significant translational motion of up to 60 mm/s for the RCA and 20 to 40 mm/s for the LAD and circumflex coronary arteries.^{7,8} The velocity of coronary artery motion increases significantly with increasing heart rates. Image acquisition of less than 50 milliseconds is truly required to completely avoid cardiac motion artifacts.⁷ Cardiac motion is minimized with the use of oral and/or intravenous β -blockers prior to scanning, thereby reducing the heart rate and prolonging the time during the cardiac cycle at which coronary artery velocity is low. Another crucial element for obtaining high-quality coronary images is to maximally dilate coronary vessels with nitroglycerin through the use of sublingual tablets or spray. Respiratory motion can be excluded by performing the scan during a breath-hold.
- 17-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 17*) Although there is still room for improvement in terms of image quality and elimination of artifacts, the diagnostic performance of the CCTA is now well established. Studies demonstrate higher diagnostic accuracy for ACS with CCTA than with other previously studied modalities, including exercise treadmill, stress nuclear imaging, and stress echocardiography. The high negative predictive value of CCTA makes 64-slice MDCT a valuable tool in the exclusion of obstructive CAD. Therefore, CCTA is useful in the risk stratification of symptomatic patients and can reduce the need for invasive diagnostic coronary angiography in patients without obstructive CAD. A recent scientific statement from the American Heart Association (AHA) on CCTA concluded that "CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients (class IIa, Level of Evidence: B)."⁹ In particular, CCTA is an accurate tool in the assessment of chest pain in patients with intermediate risk of CAD or in patients with uninterpretable or equivocal stress tests.¹⁰
- 17-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 17*) Imaging artifacts caused by the metallic stent limit the overall visibility of the inner lumen of a deployed stent and can potentially reduce the diagnostic accuracy of CCTA for the noninvasive evaluation of in-stent restenosis. Stent location, heart rate, and stent diameter are also important determinants of accuracy and feasibility for CCTA in this setting.
- 17-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 17*) Anomalies of the coronary arteries are reported in 0.3% to 1% of the general population.¹¹ Approximately 20% of coronary anomalies can be hemodynamically significant and manifest as arrhythmias, syncope, MI, or sudden death.^{12,13} An interarterial course between the pulmonary artery and aorta is the coronary anomaly most commonly associated with sudden cardiac death.¹⁴
- 17-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 17*) Cardiac CT is helpful in reducing the risk of coronary occlusion during TAVR. Coronary occlusion is said to occur in 0.66% of TAVR procedures and is associated with a poor clinical outcome. The mechanism of coronary occlusion relates to calcification on the native aortic valve leaflet being displaced up toward the coronary ostium. CT allows for accurate assessment of both the height of the coronaries and the size and capacity of the sinus of Valsalva.¹⁵ Evidence suggests that a left main height of < 12 mm in conjunction with shallow of Valsalva mean diameter (cusp to commissures) of < 30 mm was associated with more than a fivefold increased risk of coronary occlusion. In addition, a sinus of Valsalva-to-annular ratio of less than 1.25 was also strongly predictive of an increased risk.

- 17-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 17*) The most significant, and routinely available, radiation reduction strategy (up to 79%) can be achieved through prospective ECG-gated or sequential CCTA image acquisition, which involves the use of axial scanning with the tube current on only during prespecified portions of the cardiac cycle, eliminating tube current (milliamperere) during nonimaging portions of the cardiac cycle (ie, systole).^{16,17} Additionally, radiation exposure can be further minimized by approximately 46% to 53% by decreasing the tube voltage in nonobese (body mass index < 30 kg/m²) patients from 120 to 100 kVp.^{18,19} More recently, new iterative reconstruction algorithms have been introduced and validated for use in cardiac CT to allow for significant noise reduction, enabling an uncoupling of tube current and image noise and thereby allowing for significant tube current and dose reduction.²⁰ Finally, new scan acquisition modes employing fast helical pitch technique afforded by dual source dual detector technology allow for rapid scan acquisition and significant dose reduction as a result.²¹
- 17-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 17*) CCTA yields independent prognostic information in addition to clinical risk factors in patients with suspected or known CAD.²² In patients with chest pain, CCTA can identify obstructive lesions, such as proximal LAD stenosis, as well as the number of vessels with moderate to severe stenosis, which predict an increased risk for all-cause mortality.²³ The presence of any stenosis greater than 50% at CCTA has been associated with a 10-fold higher risk of cardiovascular events. In addition, the extent of CAD, reflected by the number of coronary segments involved, incrementally increased the risk of adverse outcomes.²⁴ Plaque morphology by CT confers incremental prognostic information beyond that provided by percent stenosis alone. CCTA measures of CAD severity and LVEF have independent prognostic value. Incorporation of CAD severity had incremental value for predicting all-cause death over routine clinical predictors and LVEF in patients with suspected obstructive CAD.²⁵
- 17-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 17*) CTA may guide the surgical approach by defining the position of the sternum to the RV, establishing patency of existing grafts, and visualizing the aorta, thereby avoiding unnecessary trauma and bleeding.²⁶ CCTA may be clinically useful for the evaluation of coronary bypass grafts and coronary anatomy in symptomatic patients.^{27,28} In the case of reoperation or revascularization, coronary CTA may provide critically important information on the status and anatomic location of the bypass grafts. The AHA Scientific Statement on CCTA states, "It might be reasonable in most cases to not only assess the patency of bypass graft but also the presence of coronary stenoses in the course of the bypass graft or at the anastomotic site as well as in the native coronary artery system (class IIb, Level of Evidence: C)."⁹

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Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2010;56(22):1864-1894.

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CHAPTER 18

Nuclear Cardiology

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 18-1.** The concept that CAD can be detected with radiopharmaceuticals used for SPECT-MPI is based on the ability to detect a relative reduction in myocardial perfusion in a region supplied by a significantly stenosed vessel when compared with a normal region during hyperemia. Which of the following factors beyond focal percent stenosis can affect the degree of hyperemia achievable in diseased vessels?
- A. Myocardial mass distal to the stenosis
 - B. Endothelial dysfunction
 - C. Nonatherosclerotic microvascular disease
 - D. B and C
 - E. A, B, and C
- 18-2.** A 55-year-old double-amputee man with a prior history of ischemic heart disease, migraine, dyslipidemia, and hypertension was admitted to the emergency department with central chest pain. His medications include bisoprolol, amlodipine, isosorbide dinitrate, aspirin, ramipril, rosuvastatin, and the over-the-counter Excedrin Migraine. Initial ECG and biomarkers were within normal limits. Three days after admission, the patient underwent stress nuclear SPECT-MPI for risk stratification. With regard to his medications, which of the following statements is *true*?
- A. Bisoprolol should be discontinued for 12 hours before stress imaging
 - B. Amlodipine should be discontinued for 12 hours before stress imaging
 - C. Isosorbide dinitrate should be discontinued for 48 hours before stress imaging
 - D. Excedrin Migraine should be discontinued for 24 hours before stress imaging
 - E. All of the above
- 18-3.** A frail 89-year-old woman with a prior history of asthma, multiple falls, peripheral vascular disease, and permanent atrial fibrillation was admitted to the hospital following an episode of retrosternal chest pain. Initial ECG and biomarkers were within normal limits. Three days after admission, the patient underwent stress nuclear SPECT-MPI. Which of the following types of stress testing is the preferred approach to stress nuclear SPECT-MPI for this patient?
- A. Adenosine
 - B. Regadenoson
 - C. Dipyridamole
 - D. Dobutamine
 - E. Exercise
- 18-4.** A 75-year-old man with a prior history of myocardial infarction, dyslipidemia, and hypertension was admitted to the hospital following an episode of central chest pain. Initial ECG showed T-wave inversion in the anterior leads with negative biomarkers. Three days after admission, the patient underwent rest thallium-201 (²⁰¹Tl) SPECT-MPI, which is illustrated in [Figure 18-1](#). Which of the following is the optimal SPECT approach for the assessment of myocardial viability in this patient?

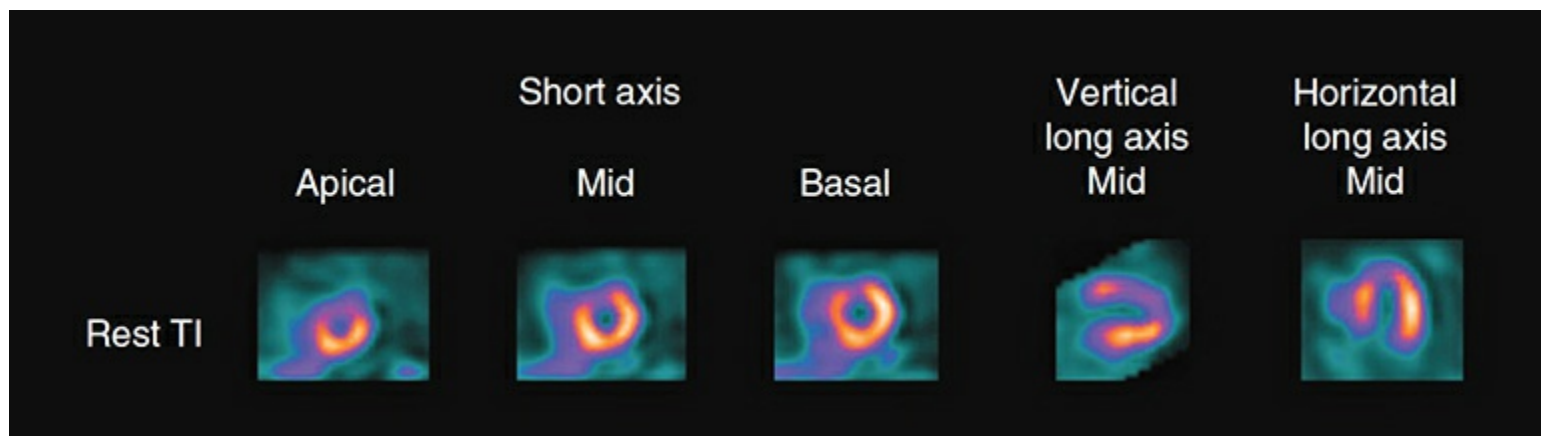


FIGURE 18-1 Rest thallium-201 (^{201}Tl) single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) showing a large amount of resting ischemia in the left anterior descending. The stress SPECT-MPI study was canceled in this patient because of the unexpected perfusion defect.

- A. Rest $^{99\text{m}}\text{Tc}$ -sestamibi SPECT-MPI
- B. Rest $^{99\text{m}}\text{Tc}$ -tetrofosmin SPECT-MPI
- C. Rest/redistribution thallium-201 (Tl) SPECT-MPI
- D. Stress SPECT-MPI
- E. Any of the above

18-5. A 65-year-old woman with multiple risk factors for coronary artery disease presented to the emergency department with 2-day history of retrosternal chest discomfort at rest. The patient, whose images are shown in Figure 18-2, was referred for SPECT-MPI after an initial normal ECG and negative biomarkers. With regard to the use of SPECT-MPI in the evaluation of acute chest pain, which of the following statements is *false*?

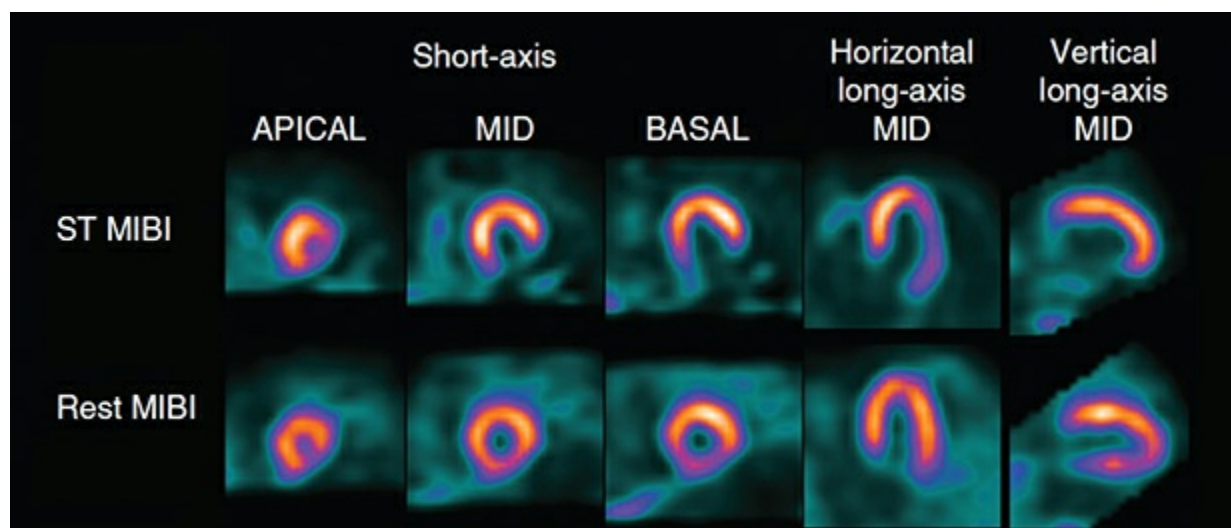


FIGURE 18-2 Adenosine stress/rest myocardial perfusion single-photon emission computed tomography images. Rest sestamibi (MIBI) demonstrated minimal (borderline) perfusion defect in the inferior wall. Stress imaging revealed evidence of severe and extensive ischemia in the inferior and inferolateral wall (41% of the left ventricle).

- A. A normal rest SPECT-MPI alone provides strong evidence of the absence of acute MI
- B. There is a reduction in hospitalizations when rest SPECT-MPI is incorporated into an ED evaluation strategy of patients presenting with suspected ACS
- C. Stress SPECT-MPI study is of no value in ruling out an ACS after a normal rest SPECT-MPI study
- D. Stress SPECT-MPI study is safe in low-risk ED patients
- E. A normal stress SPECT-MPI study is associated with a very low cardiac event rate

18-6. A 55-year-old man with a prior history of stage IV chronic kidney disease, hypertension, and dyslipidemia presented to the emergency department complaining of central chest pain. Initial ECG revealed an old LBBB, and the laboratory investigations showed negative biomarkers. Which of the following is the best imaging modality for this patient's risk assessment?

- A. Vasodilator SPECT-MPI
- B. Exercise stress SPECT-MPI
- C. CMR imaging
- D. CCTA
- E. Any of the above

18-7. A 58-year-old morbidly obese woman with a prior history of poorly controlled type 2 diabetes, peripheral vascular disease, stage IV COPD, hypertension, dyslipidemia, and rheumatoid arthritis was admitted to the emergency department with severe retrosternal chest pain. There were no new changes on the initial ECG, and the labs revealed negative biomarkers. Which of the following is the best initial imaging modality for this patient's risk assessment?

- A. Exercise stress ECG test
- B. Exercise stress CMR imaging

- C. Exercise stress nuclear MPI
- D. Vasodilator stress nuclear MPI
- E. Any of the above

18-8. Applications of nuclear MPI in stable ischemic heart disease are included in the recent ACCF/AHA clinical practice guidelines. Which of the following was assigned a class Ib level of evidence for exercise MPI?

- A. Patients with an intermediate pretest risk who have an ECG for which the exercise response cannot be interpreted
- B. Patients with an intermediate pretest risk who have an interpretable ECG
- C. Patients with ongoing chest pain and uninterpretable ECG (as in old LBBB)
- D. None of the above
- E. All of the above

18-9. Several large randomized clinical trials have evaluated the application of CCTA to patients with suspected ACS in the ED in comparison to a standard of care approach. In which of the following settings of chest pain in the ED would SPECT-MPI be preferred over CCTA?

- A. Elderly patients with known dense coronary calcification
- B. Younger patients due to the radiation exposure with CCTA
- C. Patients with documented allergy to gadolinium-based contrast agents
- D. Patients with valvular heart disease
- E. All of the above

18-10. The 2013 ACCF/AHA guideline for the management of heart failure summarized the recommendations for the use of imaging in heart failure patients. Based on this statement, in which of the following clinical applications may nuclear imaging *not* play a role?

- A. Patients with ischemic cardiomyopathy who have had a significant change in their clinical status
- B. Radionuclide ventriculography for the assessment of LVEF when device therapy is being considered
- C. Patients who received treatment that may affect cardiac function
- D. Patients with ischemic cardiomyopathy with EF < 35% who are not eligible for revascularization
- E. Radionuclide ventriculography for the assessment of LVEF and LV volumes when echocardiography is inadequate

ANSWERS

18-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 18*) Multiple factors beyond focal percent stenosis can also affect the degree of hyperemia achievable in diseased vessels. These include stenosis length, myocardial mass distal to the stenosis, plaque composition, diffuse atherosclerosis, nonatherosclerotic microvascular disease, and endothelial dysfunction.^{1,2} In general, a significant reduction in maximal hyperemia is usually present when stenosis severity exceeds 70%.³ However, when compared to assessment of fractional flow reserve (FFR), considered the gold standard, only 35% of vessels visually assessed as having 50% to 70% stenosis manifest a decrease in maximal hyperemia.⁴

18-2. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 18*) In general, for purposes of diagnosis or initial risk stratification, stress nuclear MPI is performed with the patient off anti-ischemic medications⁵ because these medications may limit the development of ischemia during the stress test. When feasible, the use of beta-blockers or long-acting calcium channel blockers should be discontinued for 48 hours before stress imaging, and long-acting nitrates should be discontinued for 12 hours before stress imaging.⁵ In general, discontinuation of compounds containing caffeine (Excedrin Migraine) for 24 hours prior to the use of adenosine or dipyridamole and 12 hours prior to the use of regadenoson is recommended.^{5,6}

18-3. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 18*) For patients who cannot exercise (mobility impairment, severe peripheral vascular disease), pharmacologic stress testing is the preferred approach to stress.⁷ The preferred pharmacologic stress agents for SPECT-MPI are coronary vasodilators: adenosine, regadenoson, or dipyridamole. Because of the potential adverse effect of severe bronchospasm, dipyridamole is contraindicated for asthmatics. Adenosine is considered contraindicated for patients with second- or third-degree AV block, sick sinus syndrome, or bronchospasm. Regadenoson has the potential to reduce the high frequency of uncomfortable systemic adverse effects and the risk of bronchospasm in asthmatics that are associated with adenosine and dipyridamole. A large phase IV study (999 patients) has reported the safety of regadenoson in patients with stable chronic obstructive pulmonary disease or asthma, but appropriate resuscitative measures should be available in case bronchospasm occurs.^{6,8} An alternative to vasodilator stress is inotropic stress with dobutamine. With the increased use of regadenoson, which has fewer contraindications, dobutamine stress nuclear MPI has markedly decreased in many nuclear laboratories. Dobutamine stress results in a lower-rate pressure product than exercise and a lower peak coronary blood flow with vasodilator stress.

Moreover, this patient has atrial fibrillation, and dobutamine may aggravate this arrhythmia.

- 18-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 18*) Although PET and MRI are considered superior for viability assessment, rest/redistribution 201Tl SPECT-MPI is the preferred SPECT approach for the assessment of myocardial viability.⁹ Theoretically, the effectiveness of 201Tl SPECT-MPI for viability assessment could be improved by the administration of nitroglycerin prior to the rest injection. Importantly, 24-hour imaging may show additional redistribution compared to 4-hour imaging^{10,11} because, in the setting of a critical coronary stenosis with reduced resting blood flow, the time to complete redistribution may be delayed. The stress SPECT-MPI study is not the optimal approach in this patient because of the unexpected perfusion defect at rest. Rest ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin can also be used to assess myocardial viability. However, they are not considered optimal because, unlike 201Tl, they reflect only myocardial perfusion and do not redistribute into the potassium pool. Furthermore, these agents underestimate viability in the presence of myocardial hibernation with resting hypoperfusion.
- 18-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 18*) Because of the very strong relationship between an acute MI and acute closure of a coronary artery, a normal rest MPI alone, without stress imaging, provides strong evidence of the absence of MI (option A). A 99% negative predictive value of rest SPECT-MPI alone for MI was reported in several studies beginning in the mid-1990s.¹² A prospective, randomized, controlled multicenter trial reported a reduction in hospitalizations when rest SPECT-MPI was incorporated into an ED evaluation strategy of patients presenting with suspected ACS (ERASE Trial) (option B).¹³ When the radiopharmaceutical is injected after pain has subsided and the SPECT-MPI study is normal, stress SPECT-MPI studies are commonly used to further rule out an ACS because unstable angina might be associated with normal rest perfusion (Figure 18-2). This case illustrates this concept, that is, the value of stress testing when rest MPI is normal in the acute chest pain patient (option C). In fact, rest sestamibi (MIBI) demonstrated minimal (borderline) perfusion defect in the inferior wall, while stress imaging revealed evidence of severe and extensive ischemia in the inferior and inferolateral wall. Based on extensive literature documenting the safety of maximal exercise testing in low-risk ED with a normal ECG and normal serial enzymes (4 to 6 hours apart), a normal stress SPECT-MPI study was safe and associated with a very low cardiac event rate in several studies (options D and E).¹⁴
- 18-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 18*) Current guidelines support nuclear MPI in symptomatic patients with LBBB.¹⁵ Vasodilator stress SPECT-MPI has been shown to be an excellent predictor of cardiac events in LBBB patients (option A).¹⁶ Guidelines give a class I indication for the use of pharmacologic stress nuclear MPI in the patients with LBBB, regardless of the ability to exercise to an adequate workload (options A and B).¹⁵ Nuclear MPI has a distinct advantage over the use of CMR imaging and CCTA for risk assessment of the CKD patient because there is no organ toxicity associated with the injection of the radionuclide tracers (options C and D). CMR with gadolinium contrast is contraindicated in these patients due to the risks of nephrogenic systemic fibrosis in renal failure patients. With CCTA, the nephrotoxicity of the iodinated contrast results in this study being contraindicated unless the patient is on dialysis. Even in the dialysis patient, the high CAC scores commonly found in the renal failure patient can reduce the diagnostic and prognostic value of the coronary CTA study.
- 18-7. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 18*) Patients may be categorized as unable to exercise if they are challenged with performing moderate household, yard, or recreational work.¹⁷ In addition, patients with disabling comorbidities are also unable to exercise, and they include patients who are severely frail, markedly obese, with severe peripheral arterial disease, severe chronic obstructive pulmonary disease, or orthopedic limitations. These groups form a large proportion of patients who will be referred and have appropriate indications for nuclear MPI. In patients unable to exercise, guidelines support pharmacologic stress imaging as the initial test in symptomatic male and female patients with intermediate or high pretest likelihood of CAD.^{5,18,19}
- 18-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 18*) The ACCF/AHA SIHD guideline assigned a class Ib level of evidence to exercise MPI for patients with an intermediate to high pretest risk who have an ECG for which the exercise response cannot be interpreted.²⁰ An exercise stress MPI in this same subset with an intermediate to high risk in the presence of an interpretable ECG was assigned a class IIa level of evidence. Exercise stress is not appropriate in the setting of ongoing chest pain, which may be the manifestation of a high-risk acute coronary syndrome.
- 18-9. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 18*) Coronary CTA is of value and generally preferred over SPECT-MPI in the ED setting. However, there are certain scenarios of chest pain in the ED in which SPECT-MPI would be preferred. These include patients with known dense coronary calcification (option A), often encountered in the elderly demographic, patients with prior stents causing artifacts within the stent lumen, and patients with contraindications to CCTA.²¹⁻²³ CCTA does expose the younger patient to radiation, although the dose with contemporary techniques is lower than that of SPECT-MPI. CCTA does require contrast administration, although this is iodinated contrast (not gadolinium-based contrast as is used for MRI).
- 18-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 18*) Based on the ACCF/AHA guideline for the management of heart failure, the clinical applications where imaging may play a role include:²⁴ (i) repeat measurement of LVEF in patients who have had a significant change in their clinical status, received treatment that may affect cardiac function, or are under consideration for device therapy (class I, level of evidence C); (ii) imaging to detect ischemia and viability in

patients with de novo heart failure, known CAD, and no angina, unless the patient is not eligible for revascularization (class IIa, level of evidence C); (iii) viability assessment prior to revascularization in select situations is reasonable in the heart failure patient with CAD (class IIa, level of evidence B); and (iv) radionuclide ventriculography for the assessment of LVEF and LV volumes when echocardiography is inadequate (class IIa, level of evidence C).

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CHAPTER 19

Positron Emission Tomography in Heart Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 19-1.** Although the assessment of coronary flow and coronary flow reserve (CFR) is based on absolute rather than relative measures of myocardial perfusion, these measures may still appear reduced in the absence of obstructive epicardial coronary artery disease. Which of the following factors may lower stress perfusion to erroneously low ischemic levels?
- A. Caffeine
 - B. Beta-blockers
 - C. Inadequate vasodilator stress
 - D. Small vessel disease
 - E. All of the above
- 19-2.** The radioligand ^{18}F -FDG is the most important and most widely used for the noninvasive study of the myocardium substrate's metabolism with PET. In which of the following cells does ^{18}F -FDG *not* trace glucose utilization?
- A. Mechanical heart valves
 - B. Skeletal muscle cells
 - C. Brain cells
 - D. Tumor cells
 - E. Inflammatory cells
- 19-3.** Adequate patient preparation during the 24 hours before a ^{18}F -FDG PET scan is essential for reliable results due to the myocardium's ability to shift its energy needs among several fuel substrates, including free fatty acids, glucose, and lactate. Which of the following parameters does *not* affect the myocardium's selection of fuel substrates?
- A. Concentrations of the substrates in the blood
 - B. The availability of adequate oxygenated coronary blood flow
 - C. Prior carbohydrate or fatty food intake
 - D. Hormonal influences
 - E. Neurological innervations
- 19-4.** A 71-year-old woman with a prior history of multivessel PCI and whose images are shown in [Figure 19-1](#) was referred for PET because of recent abnormal ECG and a 6-month history of exertional chest pain and dyspnea. Which of the following statements regarding the rest and stress PET images is *false*?

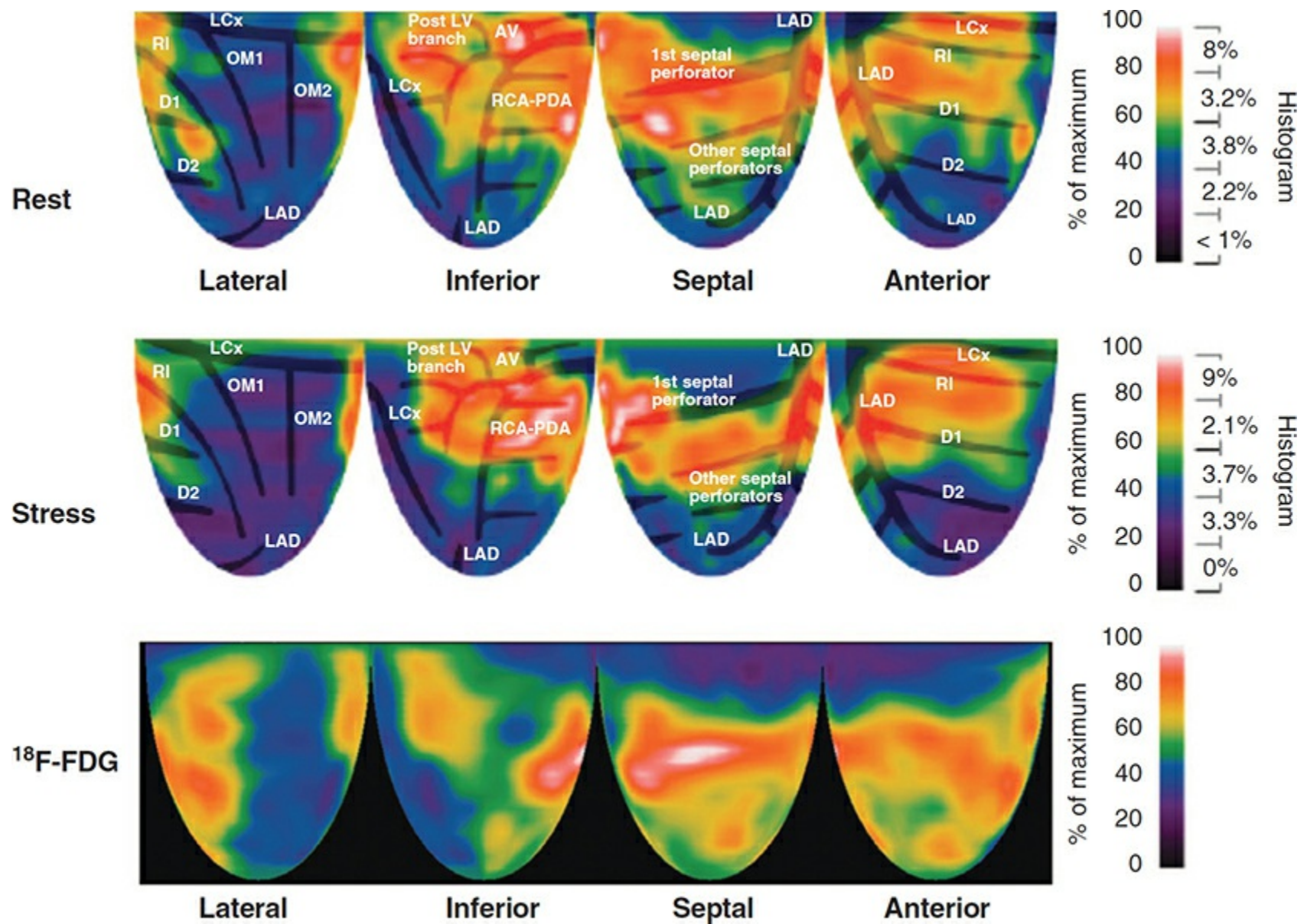


FIGURE 19-1 Relative rest and stress myocardial perfusion and ^{18}F -FDG images are color coded by the scale for relative myocardial uptake. For the rest stress relative perfusion images, the histogram on the right side of the color bar scale gives the relative activity as percent of maximum (100%) and percent of the left ventricle in each range of relative perfusion.

- A. There is resting scar or hibernating myocardium in the distribution of the left circumflex
- B. There is resting scar or hibernating myocardium in the distribution of the mid-LAD
- C. There is a significant worsening of the defect after dipyridamole (stress)
- D. There is a substantial mismatch with active FDG uptake in anterior, septal, and apical regions
- E. The lateral LV has a predominantly transmural scar

19-5. An 82-year-old hypertensive and diabetic man with prior history of multiple MIs was referred for viability PET to determine his treatment options (revascularization vs. medical treatment). Resting perfusion images are illustrated in [Figure 19-2](#). Which of the following statements regarding rest/viability PET images is *false*?

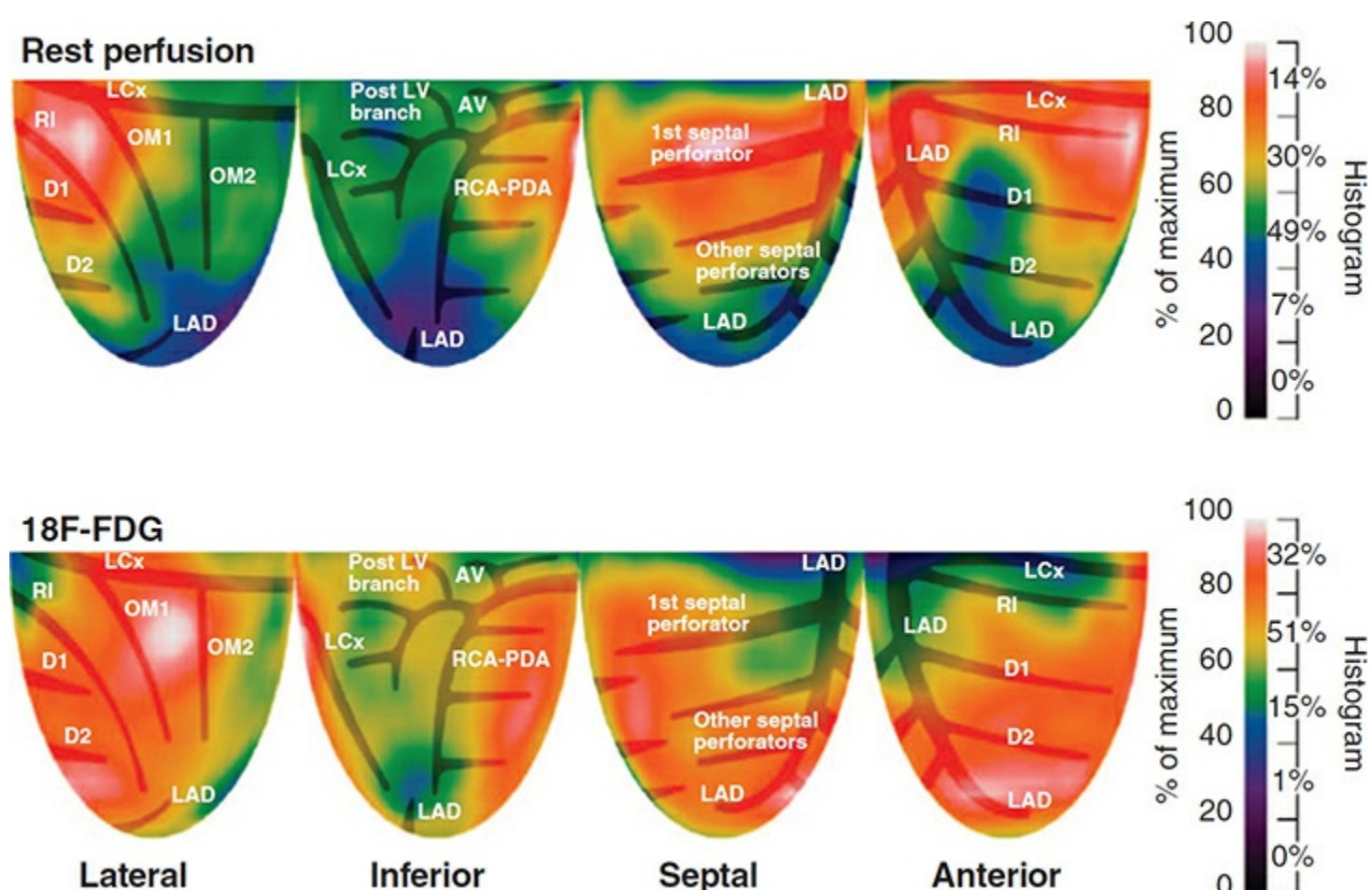


FIGURE 19-2 Relative rest perfusion and ^{18}F -FDG images are color coded by the scale for relative myocardial uptake. The

histogram on the right side of the color scale gives the percent of the left ventricle in each range of relative uptake.

- A. There are apical perfusion defects
- B. There are anterior perfusion defects
- C. There are lateral perfusion defects
- D. Most of the heart is no longer viable
- E. None of the above

19-6. An 86-year-old woman was referred for PET scan after refusing a coronary angiography when she presented to the emergency department complaining of retrosternal chest pain after an emotionally stressful event. Initial ECG revealed ischemic-appearing ST changes with elevated biomarkers. Echocardiography showed apical akinesis and hyperdynamic function of the basal segments, with an EF of 28%. Which of the following statements about the stress and rest PET perfusion and ^{18}F -FDG findings of Takotsubo stress cardiomyopathy is *true*?

- A. Stress perfusion activity is increased in the basal half of the LV
- B. ^{18}F -FDG metabolic activity is decreased in the apical half of the LV
- C. “Inverse flow metabolism mismatch” is a characteristic finding
- D. B and C
- E. A, B, and C

19-7. The assessment of myocardial viability is clinically used in patients with ischemic cardiomyopathy and severely impaired LV function in order to determine prognosis and guide therapeutic decision making. Which of the following clinical outcomes related to myocardial viability is *false*?

- A. Revascularization of viable myocardium often leads to increases in LVEF
- B. Revascularization of viable myocardium may lead to a reversal of LV remodeling
- C. Revascularization of viable myocardium is associated with relief of heart failure symptoms
- D. Postrevascularization improvements in physical activity are related to the amount of viable myocardium
- E. Revascularization of nonviable myocardium never leads to functional or prognostic improvements in patient outcomes

19-8. A 67-year-old asymptomatic man whose images are shown in [Figure 19-3](#) was referred for PET scan after an abnormal exercise stress test and coronary angiogram. The patient presented on the day of the examination after 16 hours of fasting. With regard to the PET perfusion and glucose metabolism images ([Figure 19-3](#)), which of the following statements is *false*?

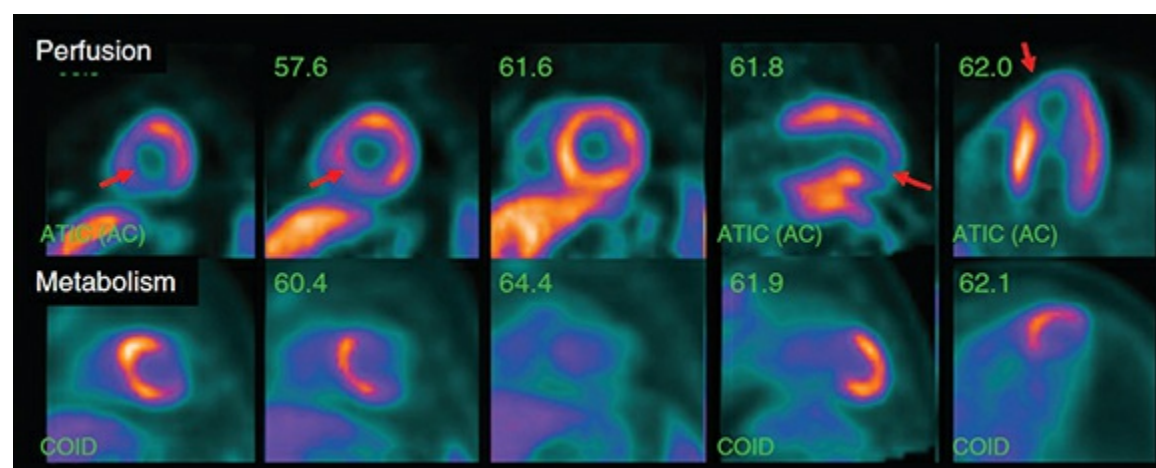


FIGURE 19-3 Positron emission tomography (PET) N-13 ammonia perfusion and glucose metabolism images.

- A. Perfusion is severely reduced in the distal anterior wall
- B. Perfusion is severely reduced in the apex
- C. Perfusion is severely reduced in the mid lateral wall
- D. ^{18}F -FDG activity is selectively increased in the region of the perfusion defect
- E. ^{18}F -FDG uptake in normal myocardium is absent as a result of prolonged fasting.

19-9. A 37-year-old African-American woman whose images are shown in [Figure 19-4](#) requested a second opinion and PET scan after series of nondiagnostic tests. She complained of a 2-month history of exertional dyspnea. Initial ECG showed a complete left bundle branch block. Echocardiography revealed a severely dilated left ventricle (LV) with an ejection fraction of 45%. Cardiac catheterization demonstrated dilatation of the LV, and the coronary arteries appeared normal. In which of the following conditions can the illustrated patterns of myocardial ^{18}F -FDG uptake occur?

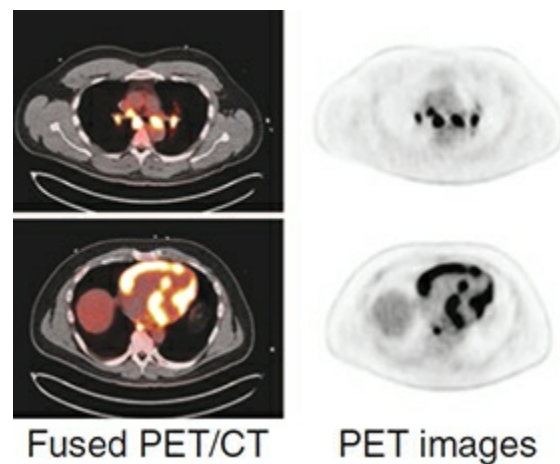


FIGURE 19-4 Axial PET-only and PET/computed tomography (CT) images of the mediastinum (upper row) and the left ventricle (lower row). Multiple foci of intensely increased ^{18}F -FDG uptake are seen in the mediastinum (consistent with mediastinal lymph node involvement) and throughout the left and right ventricular myocardium.

- A. Cardiac sarcoid
- B. Tuberculous myocarditis
- C. Epstein-Barr virus myocarditis
- D. Chagas disease
- E. All of the above

19-10. The 42-year-old man whose images are shown in [Figure 19-5](#) was referred for ^{18}F -FDG PET/CT imaging after an initial nondiagnostic transthoracic echocardiogram, which was followed by a negative transesophageal echocardiogram for vegetations. The patient had continuing fever, weight loss, and malaise. His cardiovascular examination revealed a grade 3/4 holosystolic murmur that had not been heard before. With regard to the use of ^{18}F -FDG PET/CT for the identification of infective endocarditis in this patient, which of the following statements is *false*?

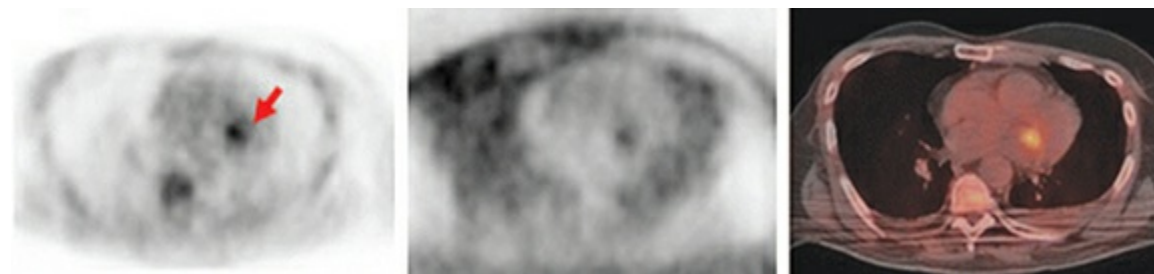


FIGURE 19-5 ^{18}F -FDG positron emission tomography (PET)/computed tomography (CT) imaging of a case of suspected infective endocarditis. The increased ^{18}F -FDG activity (arrow) corresponds to an infected mitral valve. (Reproduced with permission from Kouijzer IJ, Vos FJ, Janssen MJ, et al. The value of ^{18}F -FDG PET/CT in diagnosing infectious endocarditis, *Eur J Nucl Med Mol Imaging*. 2013 Jul;40(7):1102-1107.)

- A. Vegetations can be visualized with ^{18}F -FDG PET/CT
- B. Vegetations are seen as small foci of increased ^{18}F -FDG activity in the region of the mitral valve
- C. ^{18}F -FDG PET/CT is highly sensitive to rule out native valve endocarditis
- D. ^{18}F -FDG PET/CT may contribute to the detection of downstream septic emboli
- E. None of the above

ANSWERS

19-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 19*) Caffeine, beta-blockers, inadequate vasodilator stress, and diffuse or small-vessel disease may lower stress perfusion in cc/min/g to apparently low ischemic levels; therefore, concurrently measuring rest flow and CFR provides integrated diagnostic information for correct clinical interpretation from the coronary flow capacity map.

19-2. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 19*) As a glucose analog, ^{18}F -FDG tracks the initial transport of glucose from blood into cells and its phosphorylation to glucose-6-phosphate as the initial metabolic step of transformation of exogenously derived glucose. Because phosphorylated ^{18}F -FDG cannot be metabolized further, it is metabolically trapped in the cell, and it accumulates in tissue in proportion to rates of exogenous glucose utilization. However, the radiotracer ^{18}F -FDG is not cell specific for myocardium. It also traces glucose utilization in different organs, such as skeletal muscle and brain, as well as in tumors and inflammatory processes. While ^{18}F -FDG traces glucose utilization around prosthetic heart valves in cases of perivalvular infection, there is no utilization to trace within inert materials such as mechanical valve discs. Therefore, ^{18}F -FDG is clinically useful for imaging regional myocardial

metabolism and for identifying inflammatory disease of the cardiovascular system

- 19-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 19*) The selection of fuel substrates depends on their concentrations in blood, prior carbohydrate or fatty food intake, availability of oxygenated coronary blood flow, and hormonal influences. Complicating factors include diabetes mellitus and elevated blood catecholamine concentrations, often present in heart failure patients. Neurological innervations do not play a direct role in myocardial fuel utilization.
- 19-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 19*) The rest and stress PET images showed a large, severe, lateral, apical, mid-anterior, and distal inferior resting scar or hibernating myocardium involving 60% to 70% of the left ventricle in the distribution of the left circumflex, mid-posterior descending, and mid-left anterior descending coronary arteries. After dipyridamole, the defect was minimally worse, indicating a fixed scar or viable, low-flow, hibernating myocardium. The viability ^{18}F -FDG images showed substantial mismatch with active FDG uptake in anterior, septal, and apical regions, indicating hibernating, viable, hypoperfused myocardium in mid to distal LAD and RCA distributions comprising approximately 30% of the LV. The lateral LV had a predominantly transmural scar comprising 25% of the LV with an additional 10% of the anterior, anterolateral wall, apex, and basal inferior wall being viable and hibernating in the distribution of a large first OM branch.
- 19-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 19*) Resting perfusion images showed large, severe, anterior, apical, lateral, and inferior perfusion defects involving 60% of the LV in the distribution of the mid LAD, mid LCX, and RCA coronary arteries. ^{18}F -FDG metabolic images showed myocardial uptake of ^{18}F -FDG, indicating viability of essentially the entire heart, with only a small distal inferior nontransmural scar comprising 3% of the LV taking up less ^{18}F -FDG.
- 19-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 19*) Transient apical ballooning, called Takotsubo (stress) cardiomyopathy, may mimic an acute coronary syndrome; it affects predominantly postmenopausal women and accounts for 1% to 2% of patients with troponin-positive acute coronary syndromes but with angiographically normal coronary vessels. It has been referred to as neurogenic myocardial stunning because it often follows a stressful event.¹ Wall motion is typically impaired in the apical portion of the LV, with concordantly reduced ^{18}F -FDG metabolic activity.^{1,2} The typical finding of “inverse flow metabolism mismatch” refers to reduced apical ^{18}F -FDG metabolic activity in the presence of normal or near-normal apical perfusion.
- 19-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 19*) Patients with ischemic cardiomyopathy, severe LV dysfunction, and congestive heart failure symptoms will benefit most from the assessment of myocardial viability. Most studies have reported statistically significant postrevascularization increases in LVEF in patients with viability as compared to no or only minimal improvements in LVEF in patients without viable myocardium.³ Revascularization of viable myocardium may lead to a reversal of LV remodeling⁴ and relief of congestive heart failure symptoms.⁵ Postrevascularization improvements in physical activity are related to the amount of viable myocardium with improved physical exercise during daily life prior to and 24 months after CABG.⁶ It is important to emphasize that despite the presence of myocardial viability, even involving an adequate amount of the LV, revascularization may not always be followed by a functional improvement or reversed remodeling of the LV, and vice versa—revascularization may be associated with beneficial outcomes even in the absence of apparent viability.
- 19-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 19*) Perfusion is severely reduced in the distal anterior wall, the apex, and the distal inferior wall, suggestive of obstructive disease of the left anterior descending coronary artery. ^{18}F -FDG activity is selectively increased in the region of the perfusion defect, most likely consistent with myocardial viability; the perfusion metabolism mismatch corresponds in location to the distal left anterior descending coronary artery. ^{18}F -FDG uptake in normal myocardium is absent as a result of prolonged fasting. Among several approaches, prolonged fasting for 16 to 20 hours has been proven most effective in consistently suppressing ^{18}F -FDG uptake.⁷⁻⁹ This is due to the shift of myocardium's substrate selection from glucose to free fatty acid, thereby reducing the accumulation of ^{18}F -FDG in normal myocardium.
- 19-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 19*) Multiple foci of intensely increased ^{18}F -FDG uptake are seen in the mediastinum (consistent with mediastinal lymph node involvement) and throughout the left and right ventricular myocardium ([Figure 19-4](#)), consistent with cardiac sarcoid associated with systemic sarcoid. This pattern of focally increased myocardial ^{18}F -FDG uptake is, however, not specific for cardiac sarcoid but also occurs in other types of granulomatous and nongranulomatous inflammatory processes of the myocardium as, for example, in tuberculous myocarditis,¹⁰ Epstein-Barr virus myocarditis,¹¹ or Chagas disease.¹²
- 19-10. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 19*) There is now substantial evidence that ^{18}F -FDG PET/CT contributes to the identification of infective endocarditis, endovascular devices, and prosthetic vascular grafts, and, importantly, the detection of downstream septic emboli. Vegetations and abscesses of native and prosthetic valves can be visualized with ^{18}F -FDG PET/CT, though with a lower and clinically insufficient sensitivity (about 40%) and a specificity of about 70% to 100%.^{13,14} They are typically seen as small foci of mildly to intensely increased ^{18}F -FDG activity in the region of the mitral or aortic valve ([Fig. 19-5](#)) and do not invariably correspond to findings on

echocardiography. In one investigation in 30 patients with definite prosthetic valve infection, for example, findings by echocardiography and ^{18}F -FDG PET/CT agreed in only half of the patients; in nearly half of the remaining patients, focally increased ^{18}F -FDG uptake was seen in the valve area without corresponding vegetations on echocardiography, possibly because of an early stage of disease when echocardiography may still be negative.¹⁴ Conversely, the absence of abnormal ^{18}F -FDG uptake effectively ruled out the presence of prosthetic valve infection in that study, so the authors proposed to include PET/CT as a major criterion for the diagnosis of infective endocarditis.¹⁴

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CHAPTER 20

Cardiac Catheterization, Cardiac Angiography, and Coronary Blood Flow and Pressure Measurements

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 20-1.** The radial artery approach is associated with reduced bleeding complications and increased patient satisfaction. Which of the following factors is not an additional reason to favor the right radial artery approach over the femoral artery approach?
- A. Easy access
 - B. Direct cannulation of left internal mammary artery grafts in patients with prior coronary bypass
 - C. Most secure hemostasis in fully anticoagulated patients
 - D. Radial artery occlusion is generally well tolerated
 - E. Superficial location
- 20-2.** A 68-year-old man with prior reactions to contrast media, history of type 2 diabetes, chronic kidney disease, and left ventricular systolic dysfunction presented to the emergency department with a 2-hour history of retrosternal chest pain. ECG on arrival showed ST-elevation in interior leads, and the patient was emergently taken to the cardiac catheterization laboratory for primary PCI. Which of the following radiographic contrast agents will be preferred in this case?
- A. Iodixanol
 - B. Diatrizoate
 - C. Iothalamate
 - D. Metrizoate
 - E. Iopamidol
- 20-3.** A 75-year-old woman with a prior history of uncontrolled type 2 diabetes and stage IV chronic kidney disease was admitted to the emergency department complaining of central chest pain and dyspnea. Initial ECG showed T-wave inversions in high lateral leads, and biomarkers were above the upper limit of normal. The patient was brought to the catheterization laboratory within 24 hours. Which of the following pharmacologic regimens has recently been demonstrated to perform better than volume loading with normal saline in reducing the risk for contrast-induced nephropathy (CIN)?
- A. IV bolus of furosemide immediately before the procedure
 - B. Continuous IV furosemide infusion throughout the procedure
 - C. IV mannitol
 - D. Calcium channel blockers
 - E. None of the above
- 20-4.** Intracoronary optical coherence tomography (OCT) is a catheter-based optical imaging modality that produces high-resolution cross-sectional images of the coronary wall. OCT has superior resolution as compared to intravascular ultrasound (IVUS) for all of the following features of the vulnerable plaque, *except*:
- A. Plaque rupture
 - B. Thin-capped fibroatheroma
 - C. Macrophages within the fibrous caps
 - D. Plaque burden
 - E. Intracoronary thrombus
- 20-5.** Myocardial blood flow has been assessed angiographically using the thrombolysis in myocardial infarction (TIMI) score for qualitative grading of coronary flow. Which of the following TIMI flow grades is *false*?
- A. Flow equal to that in noninfarct arteries (TIMI-3)
 - B. Delayed or sluggish antegrade flow with complete filling of the distal coronary bed (TIMI-2)

- C. Filling beyond the culprit lesion but faint antegrade flow with incomplete filling of the distal coronary bed (TIMI-1)
- D. No flow beyond the occlusion (TIMI-0)
- E. Flow faster than that in noninfarct arteries (TIMI-4)

20-6. Unlike fractional flow reserve (FFR), coronary flow reserve (CFR) is subject to variations in hemodynamics that may alter resting flow and limit maximal hyperemic flow. Which of the following clinical situations *cannot* affect CFR?

- A. Tachycardia
- B. Dyslipidemia
- C. Diabetes
- D. Age
- E. Hypertension

20-7. An 85-year-old woman with a prior history of poorly controlled type 2 diabetes presented to the emergency department complaining of a 2-hour duration substernal chest pain and dyspnea. The initial ECG showed ST-elevation in the high lateral leads. The physical examination revealed a harsh, pansystolic murmur, loudest at the apex and radiating to the axilla. The patient was brought to the cardiac catheterization laboratory, and the left ventricular (LV) and left atrial (LA) pressure tracings are illustrated in [Figure 20-1](#). In which of the following conditions may large v waves *not* be present?

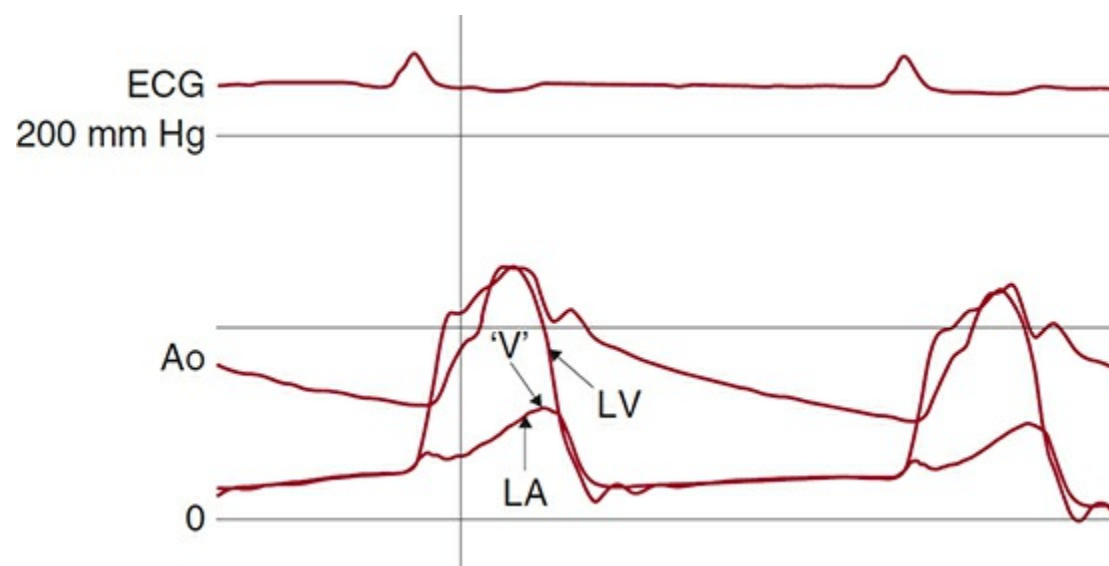


FIGURE 20-1 Left ventricular (LV) and left atrial (LA) pressures showing large V wave.

- A. Mitral regurgitation
- B. Postcardiac surgery
- C. Infiltrative heart disease
- D. Mitral stenosis
- E. None of the above

20-8. Thermodilution and Fick techniques are the most commonly used methods to assess cardiac output in the cardiac catheterization laboratory. In which of the following clinical scenarios will the thermal dilution cardiac output be unreliable?

- A. Severe tricuspid regurgitation
- B. Severe pulmonary regurgitation
- C. VSD with significant left-to-right shunt
- D. Left ventricular heart failure with low output
- E. All of the above

20-9. Valvular or vascular obstruction produces a pressure gradient across a stenosis or vascular conduit/chamber narrowing. Which of the following physiologic variables may *not* influence the pressure gradient?

- A. Serial lesions
- B. Shape of valve orifice
- C. Length of valve orifice
- D. Proximal chamber pressure
- E. None of the above

20-10. In most patients, the pulmonary capillary wedge (PCW) is sufficient to assess LV filling pressure because it closely approximates LA pressure. In which of the following conditions may PCW pressure overestimate LA pressure?

- A. Acute respiratory failure
- B. Chronic obstructive lung disease with pulmonary hypertension
- C. Pulmonary vein stenosis
- D. LV failure with volume overload
- E. All of the above

ANSWERS

- 20-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 20*) The radial approach is favored for several additional reasons: (1) The radial artery is easily accessible and is not located near significant veins or nerves; (2) the superficial artery location permits rapid and secure compression band hemostasis; (3) the radial artery access provides the most secure hemostasis in fully anticoagulated patients; (4) because of the collateral flow to the hand through the ulnar artery, the rare case of radial artery occlusion is generally well tolerated; and (5) patient comfort is enhanced by the ability to sit up and walk immediately after the procedure. However, the right radial approach is not directly amenable to cannulation of the left internal mammary artery graft for patients with prior coronary bypass.
- 20-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 20*) The advantages of the nonionic, low-osmolar agents include less hemodynamic loading, less patient discomfort, less depression of myocardial function and blood pressure, and fewer anaphylactoid reactions. Currently, nonionic, low-osmolar agents are routine for nearly all patients, and they are especially helpful in patients with poor LV function, renal disease, diabetes, or prior reactions to contrast media. Iodixanol is a nonionic, iso-osmolar dimer that is particularly well tolerated and used selectively in patients with peripheral arterial procedures and prior contrast reactions. Diatrizoate, iothalamate, and metrizoate (options B, C, and D) are all high-osmolar ionic contrast agents, whereas iopamidol (option E) is a low-osmolar nonionic contrast agent.
- 20-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 20*) Dehydrated patients or those with diabetes or renal insufficiency are at risk for CIN. Advanced precautions to limit CIN include hydration, minimizing contrast delivered, and maintenance of large-volume urine flow (> 200 mL/h). These patients should be hydrated intravenously the night before the procedure. After the contrast study, intravenous fluids should be liberally continued unless intravascular volume overload is a problem. Furosemide, mannitol, and calcium channel blockers are not helpful in reducing CIN. No pharmacologic regimen has been demonstrated to perform better than volume loading with normal saline (options A, B, C, and D).
- 20-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 20*) Compared to IVUS, OCT has superior resolution to evaluate certain features of the vulnerable plaque, such as plaque rupture, intracoronary thrombus, thin-capped fibroatheroma, and macrophages within the fibrous caps. For stent placement, OCT can visualize stent malapposition and tissue protrusion after stenting and neointimal hyperplasia at late follow-up. OCT may replace IVUS for certain applications, such as assessing stent deployment. However, compared to IVUS, OCT has inferior depth of penetration and is therefore less suited to assess total plaque burden.
- 20-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 20*) TIMI flow grades 0 to 3 have become a standard description of angiographic coronary blood flow in clinical trials. There is no TIMI flow grade 4. In acute myocardial infarction trials, TIMI grade 3 flows have been associated with improved clinical outcomes. The four grades of flow are described as follows:¹
1. Flow equal to that in noninfarct arteries (TIMI-3)
 2. Distal flow in the artery less than in noninfarct arteries (TIMI-2)
 3. Filling beyond the culprit lesion but no antegrade flow (TIMI-1)
 4. No flow beyond the total occlusion (TIMI-0)
- 20-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 20*) Tachycardia increases basal flow; therefore, CFR is reduced by 10% for every 15 heartbeats.² Increasing mean arterial pressure reduces maximal vasodilatation, thus reducing hyperemia with less alteration in basal flow. CFR may be reduced in patients with essential hypertension or aortic stenosis, myocardial ischemia, and diabetes. The variability in CFR in nonobstructed arteries may also be due to age.³ Dyslipidemia has no direct physiological effect on CFR.
- 20-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 20*) The v wave on an LA or PCW pressure tracing usually is associated with significant mitral regurgitation (Fig. 20.1). However, large v waves are neither highly sensitive nor specific for mitral regurgitation. Large v waves also may be present with mitral stenosis with or without mitral regurgitation or any condition in which the LA volume (eg, VSD or LA pressure relationship [the stiffness or compliance] is increased [such as in rheumatic heart disease, postcardiac surgery, and infiltrative heart diseases]).
- 20-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 20*) If severe tricuspid or pulmonary regurgitation or significant left-to-right shunting is present, the indicator (temperature loss) is attenuated, and the downslope of the temperature curve is prolonged, so the thermal dilution cardiac output will be unreliable. In general, when one uses thermal dilution, a true directional change in cardiac output is reflected by an observed change of $\pm 10\%$. Thermodilution is also inaccurate in patients with low cardiac output.
- 20-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 20*) The pressure gradient is influenced by physiologic variables such as rate of blood flow (eg, cardiac output, coronary blood flow); resistance to flow; proximal chamber pressure and compliance; and anatomic variables, such as shape and length of valve orifice, tortuosities of the vessels (for arterial stenosis), or multiple or serial lesions (for both cardiac valves and arterial stenosis).

20-10. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 20*) PCW pressure closely approximates LA pressure. PCW pressure overestimates LA pressure in patients with acute respiratory failure, chronic obstructive lung disease with pulmonary hypertension, pulmonary vein stenosis, or LV failure with volume overload.

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CHAPTER 21

Coronary Intravascular Imaging

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 21-1.** The echogenicity and texture of different tissue components may exhibit comparable acoustic properties. Which of the following items may *not* appear as an echolucent intraluminal image?
- A. Thrombus
 - B. Coronary calcification
 - C. Atheroma with a high lipid content
 - D. Retained contrast
 - E. Air bubble
- 21-2.** Most mechanical limitations of IVUS imaging are specific to the construct of each system. Which of the following parameters is a common cause of nonuniform rotation distortion (NURD) artifacts?
- A. Tortuosity
 - B. Small guide lumen size
 - C. Slack in the catheter shaft
 - D. Tightened hemostatic valve
 - E. All of the above
- 21-3.** Studies comparing optical coherence tomography (OCT) with IVUS suggest that time domain (TD)-OCT is safe and can be performed with success rates at least comparable to those of IVUS. Which of the following adverse effects are *not* empirically associated with the OCT procedure?
- A. Chest discomfort
 - B. Tachycardia
 - C. ST-T changes on electrocardiography (ECG)
 - D. Decompensated heart failure
 - E. All of the above
- 21-4.** Some image artifacts are common to both OCT and IVUS. Which of the following artifacts is specific to the new generation of Fourier-domain (FD-OCT) systems?
- A. Foldover artifact
 - B. Sew-up artifact
 - C. Multiple reflection artifact
 - D. Saturation artifact
 - E. Attenuation artifact
- 21-5.** Near-infrared spectroscopy (NIRS) is a new imaging modality able to detect necrotic core invasively. All of the following limitations of NIRS have considerably reduced its application in the clinical arena, *except*:
- A. Inability to quantify plaque burden
 - B. Inability to assess plaque vulnerability
 - C. Inability to visualize lumen and outer vessel wall
 - D. Inability to detect neovascularization
 - E. Inability to detect microcalcification
- 21-6.** Understanding of the structure of a normal coronary artery is essential to identify its pathologic conditions. Which of the following statements about coronary artery wall is *false*?

- A. Normal coronary artery wall appears as a three-layer structure on IVUS
 - B. A trilayered appearance by IVUS suggests the presence of intimal thickening
 - C. Visualization of the perivascular structures is common with IVUS
 - D. Visualization of the perivascular structures is not possible with OCT
 - E. Normal coronary artery wall appears as a three-layer structure on OCT
- 21-7.** The presence, depth, and circumferential distribution of calcification are important factors for selecting the type of interventional device and estimating the risk of vessel dissection and perforation during PCI. Which of the following statements about the detection of calcification is *false*?
- A. IVUS can detect the leading edge of calcium as well as determining its thickness
 - B. IVUS is superior to fluoroscopy at detecting coronary calcification
 - C. OCT can depict calcification within plaques as well as quantifying calcium burden
 - D. OCT is superior to IVUS at estimating calcium component and extent
 - E. OCT can detect superficial microcalcifications
- 21-8.** Pathologic studies have suggested a relationship between positive vessel remodeling and plaque vulnerability. Which of the following parameters is *not* characteristic of vessels with positive remodeling?
- A. Paucity of smooth muscle cells
 - B. Thinner media
 - C. Thicker cap
 - D. Larger lipid cores
 - E. Increased inflammatory marker concentrations
- 21-9.** Several IVUS studies have been performed to define predictors of restenosis after balloon angioplasty. Which of the following processes is the most important mechanism of long-term failures of nonstented coronary interventions?
- A. Negative remodeling
 - B. Positive remodeling
 - C. Neointima hyperplasia
 - D. Neointima thickening
 - E. None of the above
- 21-10.** Several studies have explored the accuracy of intravascular imaging at detecting hemodynamic significant stenosis. Which of the following parameters may *not* affect the hemodynamic implications of a stenotic lesion?
- A. The IVUS minimum luminal cross-sectional area (MLA)
 - B. Length of the stenosis
 - C. Physiology of the microvascular bed
 - D. None of the above
 - E. All of the above

ANSWERS

- 21-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 21*) The similar appearance of different materials represents an inherent limitation of all gray-scale IVUS systems. An echolucent intraluminal image, for instance, may represent thrombus, atheroma with a high lipid content, retained contrast, or an air bubble. Calcified structures are, conversely, very echobright.
- 21-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 21*) Common causes of NURD are tortuosity; severely stenotic segments; small guide lumen size; and guide catheters with sharp secondary curves, slack in the catheter shaft, or tightened hemostatic valve.
- 21-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 21*) The most frequent complication with TD-OCT using the occlusive OCT technique is transient chest discomfort, bradycardia or tachycardia, and ST-T changes on ECG, all of which tend to resolve immediately after the procedure.¹ Similar transient events were also seen during IVUS imaging procedures. Decompensated heart failure is not a reported complication of the OCT procedure.
- 21-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 21*) Foldover artifact is specific to the new generation of FD-OCT systems and is the consequence of the “phase wrapping” or “alias” along the Fourier transformation when structure signals are reflected beyond the field of view. This can occur at the site of bifurcations or in large vessels. Sew-up, multiple reflection, saturation, and attenuation artifacts are common to all intravascular imaging technologies.

- 21-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 21*) Extensive validation studies suggested that NIRS may be superior to IVUS in detecting lipid-rich plaques, but it has limited accuracy in characterizing their phenotype and detecting fibroatheroma (FA) and thin-cap fibroatheroma (TCFA).² Other significant limitations of NIRS that have considerably reduced its application in the clinical arena are its inability to quantify plaque burden, to visualize the lumen and outer vessel wall, and to assess plaque characteristics associated with increased vulnerability, such as plaque erosion, neovascularization, and microcalcification.
- 21-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 21*) A monolayer appearance is a common finding in normal coronary arteries, but a trilayered appearance by IVUS suggests the presence of intimal thickening.³ The IVUS beam penetrates beyond the adventitial layer, allowing visualization of the perivascular structures, including the cardiac veins and the pericardium. In contrast, the normal coronary artery wall (< 1.5 mm thick) appears as a three-layer structure on OCT, but imaging beyond the adventitial layer is not possible.
- 21-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 21*) IVUS detects only the leading edge of calcium and cannot determine its thickness. Thus, calcification on IVUS is usually described based on its circumferential angle (arc), longitudinal length, and depth. IVUS has shown significantly higher sensitivity than fluoroscopy in the detection of coronary calcification.⁴ OCT can depict calcification within plaques as well-delineated, low-backscattering heterogeneous regions. In addition to circumferential angulation, depth, and longitudinal length, OCT can quantify calcium burden. OCT allows more accurate estimation of the calcium component than IVUS, which significantly underestimates its extent.⁵ Superficial microcalcifications can also be identified on OCT images as small calcific deposits separated from the lumen by a thin tissue layer.
- 21-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 21*) Vessels with positive remodeling showed increased inflammatory marker concentrations, larger lipid cores, a paucity of smooth muscle cells, and medial thinning.^{6,7}
- 21-9. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 21*) One of the main contributions of intravascular imaging to this field was the realization that negative remodeling, not neointimal hyperplasia, was the most important mechanism of long-term failures of nonstented coronary interventions, namely restenosis. This was initially demonstrated in the peripheral vessels and later reported in the coronary circulation.⁸ These studies revealed that more than 70% of lumen loss was attributable to the decrease in external elastic membrane (EEM) area; the neointima accounted for only 23% of the loss.
- 21-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 21*) The limited value of intravascular imaging in detecting flow-limiting lesions should be attributed to the fact that the hemodynamic implications of a stenosis depend not only on MLA but also on the length of the stenosis and the physiology of the microvascular bed, which cannot be assessed by imaging techniques.

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CHAPTER 22

Magnetic Resonance Imaging and Computed Tomography of the Vascular System

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 22-1.** A rare, albeit serious, risk of contrast-enhanced magnetic resonance angiography (CE-MRA) is the association between gadolinium-based contrast agents and nephrogenic systemic fibrosis. In which of the following scenarios may the linear chelates of gadolinium be considered safe?
- A. Chronic renal impairment with $\text{eGFR} < 30 \text{ mL/m}^2$
 - B. Acute renal impairment
 - C. Perioperative liver transplantation
 - D. Neonates
 - E. Severe heart failure
- 22-2.** Before the advent of CE-MRA, nonenhanced magnetic resonance time of flight (TOF) imaging acquisitions were used to image the carotid arteries, demonstrating good agreement with digital subtraction angiography (DSA). Which of the following statements about the limitations of TOF imaging is *false*?
- A. It is sensitive to turbulent flow
 - B. It tends to underestimate the severity of stenoses
 - C. It has long acquisition times
 - D. It increases the potential for motion artifacts
 - E. None of the above
- 22-3.** A 67-year-old man with a prior history of uncontrolled hypertension presented to the emergency department complaining of an acute-onset excruciating and sharp retrosternal chest pain while watching a football game on television. Initial ECG revealed normal sinus rhythm with nonspecific ST changes in the lateral leads. Cardiac biomarkers were within normal limits, and a chest radiography showed moderate mediastinal widening. Which of the following imaging modalities has the highest sensitivity and specificity for detecting this condition?
- A. MRI
 - B. Retrograde invasive aortography
 - C. Transthoracic echocardiography
 - D. Transesophageal echocardiography
 - E. They all have the same sensitivity and specificity for detecting this condition
- 22-4.** Thoracic aortic aneurysms (TAAs) are typically discovered in asymptomatic patients, with symptoms occurring in the setting of either a complication of the disease (eg, a rupture or dissection) or when these complications are imminent. Which of the following statements about the recommendations for surgery is *false*?
- A. Diameter of the ascending aorta $> 50 \text{ mm}$ is the threshold for degenerative aneurysm
 - B. Diameter of the ascending aorta $> 50 \text{ mm}$ is the threshold for aneurysm associated with bicuspid aortic valve
 - C. Diameter of the ascending aorta $> 50 \text{ mm}$ is the threshold for aneurysm associated with Marfan disease
 - D. Thresholds can be lowered in case of rapid expansion of TAA ($> 5 \text{ mm/y}$)
 - E. Thresholds can be lowered in select connective tissue diseases (eg, Loeys-Dietz syndrome)
- 22-5.** A 77-year-old man with a prior history of hypertension, type 2 diabetes, and a 150-pack-per-year tobacco smoking habit presented to his cardiologist for a health maintenance examination. He has been feeling generally well and has no particular complaints or concerns. On physical examination, there was an extensive palpable pulsatile abdominal mass. Which of the following represents the preferred imaging modality for preoperative evaluation of abdominal aortic aneurysms (AAA)?

before open or endovascular surgery?

- A. CTA
- B. Ultrasonography
- C. TOF sequences MRI
- D. CE-MRA
- E. Digital subtraction angiography

22-6. A 55-year-old man with a prior history of poorly controlled type 2 diabetes, hypertension, and a 100-pack-per-year tobacco smoking habit, presented to the emergency department with a 6-month history of leg pain upon exertion. He noticed that he had bilateral calf pain (worse on the left) with walking and that it tended to go away when he stopped walking. Which of the following is the best initial investigation for this patient's complaint?

- A. Ultrasound imaging
- B. Ankle brachial pressure index
- C. CTA
- D. TOF imaging
- E. CE-MRA

22-7. The diagnostic accuracy of CTA for the evaluation of peripheral vessels compares well with MRA and invasive angiography. Which of the following clinical settings does *not* represent one of the main clinical indications of CTA for imaging the lower extremities?

- A. Evaluation of arterial and aneurysmal disease
- B. Evaluation of patency and integrity of bypass grafts
- C. Traumatic arterial injury
- D. Acute ischemia
- E. None of the above

22-8. Plaques that are at high risk for rupture represent a potential imaging target for identifying vulnerable patients likely to develop unstable manifestations of their atherosclerotic disease. Which of the following features is *not* a key characteristic of vulnerable plaques?

- A. A fibrous cap with thickness between 65 μm and 85 μm
- B. Few smooth muscle cells
- C. Heavy infiltrate of inflammatory cells
- D. Microcalcification
- E. Large necrotic core

22-9. A key advantage of MRI of the vasculature is the soft-tissue contrast it provides, allowing detailed examination of the composition of individual atherosclerotic plaques. Which of the following features of atherosclerotic plaques *cannot* be directly assessed by MRI?

- A. Intraplaque hemorrhage
- B. Calcification
- C. Luminal thrombosis
- D. Angiogenesis
- E. Fibrous cap

22-10. ^{18}F -fluoride is a PET tracer increasingly being used to measure the activity of calcific processes in the vasculature. Which of the following statements about ^{18}F -fluoride is *false*?

- A. Preferentially binds regions of vascular microcalcification activity
- B. The sensitivity of ^{18}F -fluoride/PET is superior to CT for detecting vascular microcalcification
- C. Can identify patients with increased metabolic activity in their coronary arteries
- D. Can prospectively identify the individual lesions responsible for coronary events
- E. None of the above

ANSWERS

22-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 22*) Different gadolinium contrast agents have been divided into low, medium, and high risk for causing nephrogenic systemic fibrosis¹ by the European Medicines Agency. High-risk agents include the linear chelates of gadolinium, and these are contraindicated in patients with an eGFR < 30

mL/m², acute renal impairment, and perioperative liver transplantation, as well as in neonates. Low-risk agents include newer cyclic preparations of gadolinium. These are considered safe in patients with an eGFR of more than 30 mL/m², and they can be used in patients with an eGFR below this threshold if the benefit of undergoing contrast MRI outweighs the risk. The volume of contrast agent used in this case should be minimized and repetition within 7 days avoided.² Gadolinium contrast agents are routinely used, and known to be safe, in the evaluation of patients with (often severe) forms of heart failure.

- 22-2. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 22*) TOF acquisitions are sensitive to turbulent flow, can overestimate stenoses, and have long acquisition times, increasing potential motion artifacts.² Although TOF MRA remains useful for patients with contraindications to MRI contrast, such as renal insufficiency, CE-MRA has become the technique of choice for imaging the carotid arteries.
- 22-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 22*) Of all the imaging techniques, MRI has the highest sensitivity and specificity for detecting aortic dissection (98%).⁴ However, the use of MRI for the detection of aortic dissection is limited by its lack of availability in urgent situations and by the difficulty of monitoring and managing critically ill patients in the MRI scanner. Therefore, CTA is now considered the mainstay for the accurate and timely diagnosis of acute aortic syndromes.⁵ Retrograde invasive aortography has an overall sensitivity of 88% and specificity of 94% for the detection of aortic dissection.^{6,7} Transesophageal echocardiography, like CTA and MRA, has demonstrated high accuracy for the diagnosis of aortic dissection and is an alternative diagnostic technique.⁸ Transthoracic echocardiography can, in most cases, visualize the aortic root and proximal ascending aorta, but it is not sufficiently comprehensive to rule out this diagnosis.
- 22-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 22*) When the diameter of the ascending aorta is > 55 mm for degenerative aneurysm (option A) and > 50 mm for aneurysm associated with bicuspid aortic valve (option B) or Marfan disease (option C), surgery is recommended.⁹ These thresholds can be lowered in case of rapid expansion of TAA (> 5 mm/y) or in select connective tissue diseases (eg, Loeys–Dietz syndrome) (options D and E).
- 22-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 22*) Preoperative assessment of AAAs before open or endovascular repair should include determination of the maximum transverse diameter; the relation of the AAA to the renal arteries; the length, diameter, and angulation of the normal-caliber aorta below the renal arteries before the aneurysm (ie, the infrarenal neck); the presence of iliac or hypogastric aneurysms; and serious occlusive disease in the iliac or renal arteries. CTA represents the preferred imaging modality for preoperative evaluation of AAAs before open or endovascular surgery because it allows precise assessment of each of the aforementioned parameters. Ultrasonography remains the most cost-effective imaging technique for detection and follow-up of abdominal AAA expansion. MRI (TOF sequences, CE-MRA) represents an alternative to CTA for the preoperative evaluation of AAA, particularly in cases of renal insufficiency or advanced arterial calcification, although attention should be paid to the risk of developing nephrogenic systemic fibrosis following gadolinium administration in patients with the former. Digital subtraction angiography (DSA) has been largely replaced by the preceding imaging modalities.
- 22-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 22*) The most common initial investigation in patients presenting with suspected peripheral arterial disease is the ankle brachial pressure index. This is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery. An ankle brachial pressure index of 0.90 or less should then prompt further investigation to confirm a diagnosis of peripheral artery disease. This is commonly performed with either CTA or MRA.¹⁰
- 22-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 22*) The main clinical indications of CTA for imaging the lower extremities include the evaluation of arterial and aneurysmal disease, patency and integrity of bypass grafts, traumatic arterial injury, and acute ischemia.¹¹
- 22-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 22*) Plaques that are at high risk for rupture usually have several key characteristics, consisting of a thin fibrous cap (< 65 μm) with few smooth muscle cells and a heavy infiltrate of inflammatory cells, principally macrophages, microcalcification, and a large necrotic core accounting for more than half of the volume of the plaque. Each of these characteristics therefore represents a potential imaging target for identifying high-risk plaques.
- 22-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 22*) MRI is useful in detecting intraplaque hemorrhage (option A), a process believed to play a key role in triggering plaque rupture and growth.¹² T2*-weighted sequences have been used to accurately image intraplaque hemorrhage in carotid atherosclerotic plaques.^{13,14} Plaque hemorrhage and luminal thrombosis can also be detected on T1-weighted imaging as high-intensity plaques (option C).^{15,16} Late gadolinium enhancement detects areas of interstitial edema, angiogenesis, and fibrosis (option D).¹⁷ Late gadolinium enhancement can also improve the visualization of the atherosclerotic fibrous cap, allowing estimation of the carotid cap thickness and the size of its necrotic core (option E).¹⁸ Given that calcification is hypointense on the various MRI sequences, plaque calcification is better assessed by CT and other modalities (option B).
- 22-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 22*) ¹⁸F-fluoride¹⁹⁻²⁰ preferentially binds regions of vascular

microcalcification activity.²¹ These are beyond the resolution of CT, a technique that instead detects macroscopic calcium deposits. ¹⁸F-fluoride can identify patients with increased metabolic activity in their coronary arteries, and it retrospectively appears to identify the individual lesions responsible for coronary events.²²

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SECTION 4

Systemic Arterial Hypertension

CHAPTER 23

Epidemiology of Hypertension

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 23-1.** A 48-year-old man presents in follow-up to your outpatient clinic. He has no comorbidities apart from right knee osteoarthritis and obesity. His blood pressure on his initial visit with you was 136/86 mm Hg. After losing 5 lb, today's blood pressure is 132/80 mm Hg. This patient's blood pressure can be labeled:
- A. White coat hypertension
 - B. Benign hypertension
 - C. Isolated systolic hypertension
 - D. Prehypertension
 - E. Pseudohypertension
- 23-2.** Which of the following statements about prehypertension is *false*?
- A. The lifetime risk of hypertension approaches 50%, warranting the importance of recognizing the concept of prehypertension to promote lifestyle changes to prevent the onset of hypertension
 - B. In persons without cardiovascular disease or cancer, the prevalence of prehypertension is 36%, and it is higher in men than in women
 - C. Prehypertension is associated with abnormalities of cardiac structure and function
 - D. Approximately 15% of BP-related deaths from coronary heart disease occur in individuals with BP in the prehypertensive range
 - E. Persons with prehypertension have a 43% higher risk of incident coronary heart disease than those with optimal blood pressure (< 120/80 mm Hg)
- 23-3.** A 56-year-old woman is referred to you for workup of glaucoma. Despite her blood pressure being normal in your office, her home readings have all been above 135/85 mm Hg. Regarding this particular type of hypertension, which of the following is *true*?
- A. It is present in approximately 5% of patients not receiving antihypertensive treatment
 - B. There is a twofold greater risk of future cardiovascular events in those with this type of hypertension as compared to normotensive persons
 - C. Home BP monitoring is the standard for diagnosing this type of hypertension
 - D. It is more common in younger persons
 - E. Persons with prehypertension are less likely to have this type of hypertension
- 23-4.** A 65-year-old man is referred to you from his family physician for the management of hypertension. On history, he admits to snoring when sleeping and describes daytime fatigue. On exam, BP in both arms is 164/98, HR 86 O₂ sat 96% on RA. Normal heart sounds are present, and lungs are clear to auscultation. Which of the following statements is *false*?
- A. The most common curable form of hypertension is sleep apnea
 - B. Treatment with a CPAP mask is most likely indicated
 - C. Both sleep apnea and hypertension are closely linked to obesity
 - D. Approximately 60% of sleep apnea patients are hypertensive
 - E. Approximately 25% of hypertensive patients have sleep apnea
- 23-5.** There is a fundamental difference between the genesis of hypertension in younger and older patients. Which of the following does *not* represent a true difference?
- A. In general, the systolic and diastolic BPs are increased in younger patients, whereas in people aged 60 years and older, the diastolic BP starts to fall, but there is a marked increase in systolic BP
 - B. Younger patients will have an increased peripheral resistance with a normal cardiac output, whereas older patients will

- have a selective increase of systolic BP as a result of increased arterial stiffness
- C. In younger patients, the increased peripheral resistance is a result of active vasoconstriction that is mediated hormonally, particularly by the sympathetic nervous system and the renin-angiotensin system
- D. The benefits of treatment in older patients with systolic pressures below 160 mm Hg remain unproven
- E. There is some evidence for BP treatment of the very old (age 85 years or older) to improve mortality

23-6. You are going to counsel your 55-year-old female patient on her risk factors for hypertension. Which of the following statements is *false*?

- A. The diastolic pressure will typically increase up to the age of 50, will plateau, and then will decrease throughout the remainder of the life span
- B. Increasing body mass index correlates with an increased risk of hypertension
- C. The incidence of hypertension is increased in those who smoke 15 or more cigarettes per day
- D. There is a strong positive relation between sodium intake and blood pressure
- E. Mexican Americans have prevalences that are similar to that of African Americans

23-7. The principal complications of hypertension include all of the following *except*:

- A. Left ventricular hypertrophy
- B. Peripheral arterial disease
- C. Hypothyroidism
- D. Stroke
- E. Heart failure

23-8. A 58-year-old woman with a history of untreated hypertension presents to your office to discuss the results of her cardiac echocardiogram. Which of the following would be the least likely to be found on her echocardiogram report?

- A. Diastolic dysfunction
- B. Tricuspid valve regurgitation
- C. Increased left atrial size
- D. Systolic dysfunction
- E. Left ventricular hypertrophy

23-9. Which of the following statements regarding stroke and hypertension is *incorrect*?

- A. The linear relationship between stroke and hypertension is stronger for diastolic than for systolic pressure
- B. BP typically rises acutely after a stroke, and it is postulated that this helps to maintain cerebral perfusion in the infarct's *penumbra* zone
- C. Of all the risk factors for stroke, hypertension has the highest relative risk
- D. Hypertension indirectly raises the risk of stroke through its role in atrial fibrillation and left atrial enlargement
- E. Treatment of hypertension reduces stroke rates by approximately 35% to 45%

23-10. Your 65-year-old female patient presents to the office to discuss the results of her blood work. You have been treating her for hypertension over the last 10 years. Her creatinine has risen slightly, and you are concerned. Which of the following statements is *true*?

- A. There is a twofold greater risk for end-stage renal disease with a systolic BP of > 140 mm Hg compared to a systolic BP of < 117 mm Hg
- B. Chronic kidney disease causes remodeling of the arteries and increased stiffness
- C. Hypertensive patients with mildly impaired renal function (estimated GFR < 60 mL/min) compared to normal renal function have an equivalent prevalence of target organ damage
- D. Diastolic BP is a stronger risk factor for renal death than systolic BP
- E. In a patient with chronic kidney disease, it is obvious whether the hypertension or the kidney disease came first

ANSWERS

23-1. The answer is **D**. (*Hurst's The Heart, 14th Edition, Chap. 23*). The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) 7 classification for hypertension has defined normal BP as < 120 and < 80 mm Hg. What JNC-6 previously labeled as normal (120–129 mm Hg systolic BP or 80–84 mm Hg diastolic BP) and high normal (130–139 mm Hg systolic BP or 85–89 mm Hg diastolic BP) are now combined into a single group called *prehypertension* (option D), to increase the awareness of people with an intermediate level of risk that they may progress to definite hypertension. *White coat hypertension* (or *isolated office hypertension*) (option A) is diagnosed in patients not on any BP-lowering medications when the BP is elevated only persistently in the presence of a

health care worker, particularly a physician. *Benign* hypertension, which alluded to less severe forms of hypertension, is a misnomer and is no longer used (option B). When the average systolic BP is at least 140 mm Hg or more and diastolic BP is < 90 mm Hg, the patient is classified as isolated systolic hypertensive (option C). The term *pseudohypertension* (option E) refers to a falsely elevated diastolic BP when in fact it is low. This condition represents wide pulse pressure isolated systolic hypertension in the elderly and often occurs with diabetes and diabetic kidney disease; it is associated with extensive calcification of many large arteries, including the brachial and elastic aorta.

- 23-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 23*). The lifetime risk of hypertension approaches 90%¹ (not 50%), which emphasizes the need to recognize prehypertension to help motivate physicians and patients alike to promote lifestyle modifications that will prevent or delay the transition to clinical hypertension. Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2006 in persons without cardiovascular disease (CVD) or cancer shows a prevalence of prehypertension of 36.3%, higher in men than in women, and associated with adverse cardiometabolic risk factors² (option B). Prehypertension has recently been shown to be associated with abnormalities of cardiac structure and function, specifically increased left ventricular remodeling and impaired diastolic function³ (option C). It is estimated that about 15% of BP-related deaths from coronary heart disease (CHD) occur in persons with BP in the prehypertensive range⁴ (option D). A recent meta-analysis showed that, compared with optimal blood pressure (< 120/80 mm Hg), those with prehypertension had a 43% higher risk of incident CHD (hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.26–1.63) a risk that was higher in Western subjects (relative risk [RR], 1.70; 95% CI, 1.49–1.94) than in Asian subjects (RR, 1.25; 95% CI, 1.12–1.38), with 24.1% of CHD attributable to prehypertension in Western subjects versus 8.4% in Asian subjects⁵ (option E).
- 23-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 23*). The question refers to a patient with a diagnosis of *masked hypertension*, which is defined as a normal office BP (< 140/90 mm Hg) together with an elevated daytime BP (\geq 135/85 mm Hg). The Dallas Heart Study also showed a twofold greater risk of future cardiovascular events in those with masked hypertension compared to those who were normotensive.⁶ Option A is false: masked hypertension is present in approximately 10% to 40% of patients not receiving antihypertensive treatment. Option C is false: Twenty-four-hour ambulatory BP monitoring is the standard for diagnosing masked hypertension; home BP monitoring can also be used, but it is not the standard. Masked hypertension is more common in older persons; those with mental stress; smokers; and those with metabolic syndrome, diabetes, chronic kidney disease, and obstructive sleep apnea (option D). Persons with prehypertension are *more* likely to have masked hypertension and can even develop target organ damage before transitioning to established sustained hypertension (option E).
- 23-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 23*). The most common curable form of hypertension is renal artery stenosis (not sleep apnea). Sleep apnea is emerging as one of the major causes of hypertension that is of epidemiologic significance. Support for a causal association between sleep-disordered breathing and hypertension includes physiological mechanisms involving vascular dysfunction secondary to altered sympathovagal balance and insulin resistance (option B). Both sleep apnea and hypertension are common, and unsurprisingly there are many people with both conditions. Furthermore, both are closely linked to obesity (particularly central obesity, as seen in the metabolic syndrome), so there is a cluster of related syndromes: hypertension, sleep apnea, diabetes, and the metabolic syndrome (option C). Option D: Approximately 60% of sleep apnea patients are hypertensive⁷, and, conversely, approximately 25% of hypertensive patients have sleep apnea^{8,9} (option E).
- 23-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 23*). There is evidence that in the very old (age 85 years or older), mortality may be *higher* in those with the lowest blood pressures.¹⁰ The benefit or harm of treating this patient population is currently being evaluated. In younger patients, whatever the underlying etiology of the hypertension (with a few exceptions), both systolic and diastolic BPs are raised, whereas in people aged 60 years and older, the diastolic BP starts to fall, but there is a marked increase of systolic BP (option A). The underlying hemodynamics are also different: in younger patients, the characteristic changes are an increased peripheral resistance with a normal cardiac output, whereas in older patients, the reason for the selective increase of systolic BP is increased arterial stiffness¹¹ (option B). In younger patients, the increased peripheral resistance is a result of active vasoconstriction that is mediated hormonally, particularly by the sympathetic nervous system and the renin-angiotensin system. In older patients with systolic hypertension, hormonal mediation is less important, and the changes are mostly mechanical (eg, loss of elastin fibers in the media of the arterial wall¹¹ (option C). In younger patients, it is clearly established that starting drug treatment when the pressure exceeds 140/90 mm Hg is beneficial. This may also be true in older patients, but the clinical trials that have investigated the benefits of treatment have almost all used an initial systolic BP of 160 mm Hg or greater as an entry criterion and have not lowered the pressure to below 140 or 150 mm Hg¹² (option D).
- 23-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 23*). African Americans have among the highest prevalences of hypertension compared to other major ethnic groups, and Mexican Americans have prevalences that are similar to that of whites. Age is the factor most strongly associated with hypertension. Systolic BP rises monotonically with age, whereas diastolic BP increases to about age 50, plateaus, and then decreases throughout the remainder of the life span (option A). More than 42% of those with a body mass index of 30 kg/m² or greater have hypertension, compared to 28% in those who are overweight (body mass index 25 to less than 30 kg/m²)^{13,14} (option B). Cigarette smoking has an acute effect on increasing blood pressure, primarily through stimulation of the sympathetic nervous system, with adverse effects on arterial stiffness and wave reflection (option C). Dietary sodium is implicated by many genetic,

epidemiological, migrational, and intervention studies to contribute to increasing BP in the population, and higher salt intake is likely to contribute to coronary vascular disease mainly through its effects on BP but also independently by increasing arterial stiffness and albuminuria¹⁵ (option D). The INTERSALT study involved 10,079 persons and found a strong positive relation between sodium intake and BP, with an increase of 6 g/d in salt intake estimated to elevate systolic BP 9 mm Hg over 30 years.¹⁶

- 23-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 23*). The principal complications of hypertension include coronary heart disease, left ventricular hypertrophy (option A), peripheral arterial disease (option B), stroke (option D), heart failure (option E), and chronic kidney disease. The 36-year follow-up data from the Framingham Heart Study show that while the relative impact of hypertension is greatest for stroke and heart failure (RRs, 2.6–4.0), because the overall incidence of CHD is greater than that for stroke or heart failure, the absolute impact of hypertension on CHD is greatest, even though the RR is lower (2.0–2.2).¹⁷
- 23-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 23*) There is no direct association between tricuspid regurgitation and systemic hypertension (option A). Approximately half of the patients who present with classic signs and symptoms of heart failure appear to have a normal ejection fraction of more than 50% on echocardiography, termed “diastolic dysfunction,” diastolic heart failure,” or “heart failure with preserved ejection fraction.” Diastolic heart failure is thought to be responsible for as many as 74% of cases of heart failure in hypertensive patients.¹⁸ Left ventricular hypertrophy (option E) and systolic dysfunction and heart failure (option D) are known complications of hypertension. Increased left atrial size (option C) associated with left ventricular hypertrophy can result with systemic hypertension.
- 23-9. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 23*) As with coronary events, there is a strong log-linear relationship between both systolic and diastolic pressure and stroke, although the relationship is steeper for strokes than for CHD events and much stronger for systolic than diastolic pressure.¹⁹ BP typically rises acutely after a stroke, and it is postulated that this helps to maintain cerebral perfusion in the infarct's *penumbra* zone (option B).²⁰ This forms the rationale for avoiding excessive reduction of BP immediately after a stroke. Of all the risk factors for stroke, hypertension has the highest relative risk (4.0 at 40 to 50 years, falling to 2.0 at ages 70 to 80 years), and the highest population attributable risk (40% at ages 40 to 50 years and 30% at ages 70 to 80 years) (option C). Hypertension also indirectly raises the risk of stroke through its role as an important risk factor for atrial fibrillation and left atrial enlargement, which both relate directly to stroke risk (option D). Treatment of hypertension reduces stroke rates by 35% to 44%; this has been shown in both younger patients with systolic and diastolic hypertension and in older patients with isolated systolic hypertension (option E).
- 23-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 23*) There are two main effects of CKD on the arteries: (1) increased prevalence of atherosclerosis and (2) remodeling of the arteries and increased stiffness, which has been related to increased mortality. The Multiple Risk Factor Intervention Trial showed systolic BP of > 140 mm Hg to be associated with a five- to sixfold (not twofold) greater risk for end-stage renal disease (ESRD) compared to systolic BP of less than 117 mm Hg (option A). Hypertensive patients with mildly impaired renal function (estimated GFR < 60 mL/min) have an increased prevalence of target organ damage, such as left ventricular hypertrophy, increased carotid intima-media thickness, and microalbuminuria (option C). In a large pooled cohort study of more than 500,000 individuals from the Asia-Pacific region followed for a median of 6.8 years, systolic BP was the strongest risk factor for renal death, with each standard deviation increase in systolic BP (19 mm Hg) associated with a more than 80% higher risk (HR, 1.84; 95% CI, 1.60–2.12)²¹ (option D). Although chronic kidney disease is certainly a major cause of hypertension, it is often difficult to decide whether the hypertension or the kidney disease came first because a vicious cycle can develop where one condition exacerbates the other (option E).

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CHAPTER 24

Pathophysiology of Hypertension

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 24-1.** A 52-year-old man presents to your office for prevention of cardiovascular disease. His examination is notable for a blood pressure (BP) of 153/98 mm Hg. He wants to know about factors that would predispose him to hypertension. Which of the following is *not* associated with hypertension?
- A. Excess sodium intake
 - B. Excess potassium intake
 - C. Obesity
 - D. Sedentary lifestyle
 - E. A and D
- 24-2.** A 23-year-old man is involved in a car accident and is bleeding into his abdomen. Which of the following systems *do not* regulate blood pressure (BP) acutely?
- A. Arterial baroreceptors
 - B. Chemoreceptors
 - C. Central nervous system (CNS)
 - D. Renin-angiotensin-aldosterone system (RAAS)
 - E. Increase in vasodilation
- 24-3.** Which of the following alters pressure-natriuresis in chronic hypertension?
- A. Increased tubular resorption
 - B. Decreased antinatriuretic hormones
 - C. Decreased activity of the sympathetic nervous system (SNS)
 - D. A and C
 - E. None of the above
- 24-4.** Which of the following is *not true* of the two-kidney, one-clip Goldblatt model of hypertension?
- A. The clipped kidney is at greater risk for nephron loss than the untouched kidney
 - B. The clipped kidney produces more renin than the untouched kidney
 - C. Blood flow through the untouched kidney may be increased compared to the flow before clipping of the contralateral kidney
 - D. Removal of clipping will restore blood pressure to normal levels, even after the untouched kidney becomes dysfunctional
 - E. None of the above
- 24-5.** Which of the following are *true* regarding salt-sensitive hypertension?
- A. Loss of functional nephrons contributes to salt-sensitive hypertension
 - B. High levels of Ang II or mineralocorticoids contribute to salt-sensitive hypertension by increasing renal tubular resorption
 - C. A and B
 - D. Increased sensitivity of the RAAS is associated with salt-sensitive hypertension
 - E. None of the above
- 24-6.** A 45-year-old air traffic controller presents to your office for evaluation of hypertension. Which of the following is *not true* about how the SNS contributes to hypertension?
- A. Activation of the renal sympathetic nerves causes increases in renin secretion and sodium resorption

- B. Radiofrequency renal denervation is an effective way to treat refractory hypertension
 - C. Epidemiologic studies have suggested a relationship between chronic stress and hypertension
 - D. Obesity results in increased renal sympathetic activity
 - E. Renal sympathetic activity is regulated by various regions of the brain
- 24-7.** A 58-year-old man with hypertension presents to your office to establish care. His blood pressure is well controlled with lisinopril. Which of the following is *true* about renin-angiotensin-aldosterone system (RAAS) blockade and hypertension?
- A. Blood pressure is very salt-sensitive in the setting of RAAS blockade
 - B. Angiotensin II (Ang II) elevation promotes sodium and water retention
 - C. ACE inhibitors can reduce GFR by inhibition of the constrictor effect of Ang II on efferent arterioles
 - D. RAAS blockade can prevent glomerular injury when the nephrons are hyperfiltering
 - E. All of the above are true
- 24-8.** A 55-year-old man is being treated with bevacizumab for his lung cancer. He is seeing you for management of his hypertension. Which of the following is *not true* about hypertension associated with VEGF inhibitors?
- A. VEGF-inhibitor-induced hypertension is likely to result from decreased NO
 - B. VEGF inhibition is likely to result from increased endothelin-1
 - C. VEGF-induced hypertension is solely to be mediated by its effects on the vasculature and is less likely to involve a direct effect on the kidney
 - D. All of the above are false
 - E. All of the above are true
- 24-9.** A 53-year-old woman presents with hypertension. Her serum laboratory tests are notable for hypokalemia and metabolic alkalosis. Examination is notable for the absence of acne, adiposity, or hair loss. Which is the next best diagnostic test?
- A. Dexamethasone suppression test
 - B. Plasma renin and aldosterone
 - C. Serum metanephrines
 - D. Genetic testing
 - E. None of the above
- 24-10.** A 35-year-old obese woman presents to you for evaluation of hypertension. She wants to know whether her hypertension would resolve if she were to lose weight. Which of the following is *true* about obesity and hypertension?
- A. Central adiposity is more strongly associated with hypertension than subcutaneous fat
 - B. Obesity results in increased activity of the SNS
 - C. Obesity results in activation of the RAAS
 - D. Obesity results in physical compression of the kidneys
 - E. All of the above are true

ANSWERS

- 24-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 24*) Although primary hypertension is heterogeneous, some of the main causes of high BP are known. For example, overweight and obesity may account for 65% to 75% of the risk for primary hypertension (option C). Sedentary lifestyle, excess intake of alcohol or salt, and low potassium intake are also known to increase BP in some patients (options A, B, D, and E).¹
- 24-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 24*) With rapid blood loss, three important neural control systems begin to function powerfully within seconds: (1) the arterial baroreceptors, which detect changes in BP and send appropriate autonomic reflex signals back to the heart and blood vessels to return the BP toward normal (option A); (2) the chemoreceptors, which detect changes in oxygen or carbon dioxide in the blood and initiate autonomic feedback responses that influence BP (option B); and (3) the central nervous system (CNS) (option C), which responds within a few seconds to ischemia of the vasomotor centers in the medulla, especially when BP falls below about 50 mm Hg. Within a few minutes or hours after a BP disturbance, additional controls react, including (1) a shift of fluid from the interstitial spaces into the blood in response to decreased BP (or a shift of fluid out of the blood into the interstitial spaces in response to increased BP); (2) the RAAS, which is activated when BP falls too low and suppressed when BP increases above normal (option D); and (3) multiple vasodilator systems that are suppressed when BP decreases and stimulated when BP increases above normal (option E).
- 24-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 24*) In all types of human or experimental hypertension studied thus far, there is a shift of pressure natriuresis that appears to sustain the hypertension. In some cases, abnormal

pressure natriuresis is caused by intrarenal disturbances that alter renal hemodynamics or increased tubular reabsorption (option A). In other cases, altered kidney function is caused by extrarenal disturbances, such as increased SNS activity or excessive formation of antinatriuretic hormones that reduce the kidney's ability to excrete sodium and water and eventually increase BP (options B and C). Consequently, effective treatment of patients with hypertension requires interventions that reset pressure natriuresis toward normal BP either by directly increasing renal excretory capability (eg, with diuretics), or by reducing antinatriuretic influences (eg, with RAAS blockers) on the kidneys.

- 24-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 24*) In the two-kidney, one-clip Goldblatt model of hypertension, the clipped kidney has reduced blood flow, while the untouched kidney has normal or increased blood flow (option C). This differential in blood flow results in high levels of renin being made by the clipped kidney but almost no renin from the untouched kidney (option B).¹ Over time, the untouched kidney will develop injury from the increased blood flow, leading to nephron loss (option A). Once damage has occurred to the untouched kidney, reversal of clipping will no longer be able to completely reverse hypertension (option D).
- 24-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 24*) After the loss of entire nephrons, the surviving nephrons must excrete greater amounts of sodium and water to maintain balance. This is achieved by increasing GFR and decreasing reabsorption in the remaining nephrons, resulting in increased sodium chloride delivery to the macula densa and suppression of renin release (option A). This, in turn, impairs the kidney's ability to further decrease renin secretion during high sodium intake, and BP becomes salt sensitive. Factors that increase renal tubular sodium reabsorption, such as excessive levels of mineralocorticoids or Ang II, can also cause hypertension (option B). Reduced sensitivity of the RAAS contributes to salt-sensitive hypertension (option D).
- 24-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 24*) It is widely believed that chronic stress may lead to long-term increases in blood pressure. Support for this concept comes largely from a few epidemiologic studies showing that air traffic controllers, lower socioeconomic groups, and other groups who are believed to lead more stressful lives also have increased prevalence of hypertension (option C).² Even mild increases in renal sympathetic activity stimulate renin secretion and sodium reabsorption in multiple segments of the nephron, including the proximal tubule, the loop of Henle, and distal segments (option A). Obese persons have elevated SNS activity in various tissues, including the kidneys and skeletal muscle, as assessed by microneurography, tissue catecholamine spillover, and other methods (option D). The preganglionic neurons that synapse with the renal sympathetic postganglionic fibers are located in the lower thoracic and upper lumbar segments of the spinal cord and receive multiple inputs from various regions of the brain, including the brainstem, forebrain, and cerebral cortex (option E). Whether renal denervation will prove to be an effective therapy for patients who are resistant to the usual pharmacological treatments remains to be determined (option B).
- 24-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 24*) Ang II causes salt and water retention by increasing renal sodium reabsorption through the stimulation of aldosterone secretion, by direct effects on epithelial transport, and by hemodynamic effects (option B). Blockade of the RAAS, with Ang II–receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors, increases renal excretory capability so that sodium balance can be maintained at reduced BP. However, blockade of the RAAS also makes BP salt sensitive (option A). The impairment of GFR after RAAS blockade is caused, in part, by inhibition of the constrictor effects of Ang II on efferent arterioles as well as reduced BP (option C). RAAS blockade is often beneficial when nephrons are hyperfiltering, especially if Ang II is not appropriately suppressed (option D). For example, in diabetes mellitus and certain forms of hypertension associated with glomerulosclerosis and nephron loss, Ang II blockade decreases BP, efferent arteriolar resistance, and glomerular hydrostatic pressure, and it attenuates glomerular hyperfiltration.³
- 24-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 24*) VEGF and VEGF receptors are highly expressed in the kidney. VEGF is expressed in glomerular podocytes, and VEGF receptors are present on endothelial, mesangial, and peritubular capillary cells. Signaling between endothelial cells and podocytes is thought to be important for maintenance of the filtration function of the glomerulus, and inhibitors of VEGF signaling have been shown to alter glomerular structure and function (option C). Because the endothelium is a major target for VEGF actions, it is likely that decreases in the production of endothelium-derived relaxing factors such as NO and PGs or enhanced production of vasoconstricting factors such as thromboxane and ET-1 play a role in the hypertensive response to drugs that block the VEGF pathway (options A and B).⁴
- 24-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 24*) This patient is most likely to have Conn syndrome or primary aldosteronism. Conn syndrome is manifest by expansion of extracellular fluid volume, hypertension, suppression of renin secretion, hypokalemia, and metabolic alkalosis. Therefore, testing of renin and aldosterone levels can be useful to establish a diagnosis (option B). A dexamethasone suppression test can be useful to differentiate ACTH-dependent and ACTH-independent Cushing syndrome (option A). Serum metanephrines can be useful for diagnosing pheochromocytoma (option C). Genetic testing is unlikely to be of high yield at this stage of diagnostics (option D).
- 24-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 24*) Adipose tissue distribution is important to the risk for obesity-related hypertension. Most population studies that have investigated the relationship between obesity and BP have measured BMI rather than visceral or retroperitoneal fat, which appear to be better predictors of increased BP than subcutaneous fat (option A).⁵ Additionally, three mechanisms appear to be especially important in increasing sodium reabsorption and impairing renal-pressure natriuresis in obesity hypertension: (1) increased SNS activity (option B), (2)

activation of the RAAS (option C), and (3) physical compression of the kidneys by fat accumulation within and around the kidneys and by increased abdominal pressure (option D).

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CHAPTER 25

Diagnosis and Treatment of Hypertension

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

25-1. Which of the following statements about hypertension is *false*?

- A. Hypertension is a public health problem worldwide
- B. Treating hypertension with antihypertensive drugs is effective for the long-term prevention of cardiovascular disease
- C. Normal (optimal) pressure is classified as blood pressure < 120/80 mm Hg
- D. Blood pressure measurements outside the office or clinic are always identical to office or clinic pressure measurement
- E. The prevalence of hypertension is increasing in relation to increased overweight

25-2. During a routine checkup, a 55-year-old male factory worker's recorded blood pressure is 150/90 mm Hg. What is the goal for the initial evaluation of hypertensive patients?

- A. Estimate the average blood pressure
- B. Consider the overall cardiovascular risk status
- C. Determine the presence or absence of target organ pathology
- D. Educate the patient on long-term cardiovascular risk reduction
- E. All of the above

25-3. Which of the following is considered *correct* blood pressure measurement in the clinic?

- A. Using the same cuff size for all patients
- B. Taking blood pressures in both arms, in the seated and standing positions
- C. Taking the blood pressure in one arm with the patient standing
- D. Taking the blood pressure in one arm with the patient seated
- E. Using the brachial artery pressure as a substitute for central aortic pressure

25-4. A 36-year-old woman patient has a blood pressure of 140/90 mm Hg in the clinic. An out-of-office ambulatory blood pressure monitor is requested for the next 24 hours. Which of the following is *not* an advantage of this monitoring device?

- A. It predicts the risk of morbid events better than clinic blood pressure
- B. It can diagnose white coat hypertension
- C. It can diagnose masked hypertension
- D. It eliminates the need for medical history and physical examination in determining cardiovascular disease risk
- E. It can measure systolic and diastolic pressures while the patient sleeps

25-5. After initial assessment in clinic followed by a 24-hour ambulatory pressure monitoring, a 50-year-old male banker is diagnosed with hypertension. Which of the following is *not* an appropriate course of action?

- A. Recommendation of the DASH diet
- B. Recommendation of an exercise routine
- C. Recommendation of smoking cessation and scheduled follow-up in 1 year
- D. Prescription of antihypertensive medications
- E. Performance of laboratory biochemical testing and imaging to define cardiovascular risk

25-6. Which of the following diuretics used as an antihypertensive drug does *not* cause hypokalemia as a side effect?

- A. Spironolactone
- B. Thiazides
- C. Loop-active diuretics
- D. All of the above

E. None of the above

25-7. A 62-year-old female office worker is evaluated for hypertension. She currently takes a beta-receptor blocker for angina, but due to inadequate blood pressure control, a second-line agent is being selected to achieve optimal blood pressure control. Which antihypertensive drug class is *not* appropriate to prescribe?

- A. Thiazide diuretic
- B. Non-dihydropyridine calcium channel blocker
- C. Angiotensin converting enzyme (ACE) inhibitor
- D. Angiotensin receptor blocker (ARB)
- E. Alpha-receptor blocker

25-8. Which of the following statements about hypertension management is *correct*?

- A. Beta-blockers may cause hypoglycemic unawareness
- B. The coexistence of diabetes and hypertension increases the risk of future cardiovascular disease compared to hypertension alone
- C. The incidence of new hypertension is very low in cancer patients undergoing chemotherapy treatment with vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab
- D. Once a stroke has occurred, antihypertensive drug therapy cannot help prevent additional cerebrovascular pathology and disease
- E. The prevalence and severity of hypertension are uniform across different ethnic groups

25-9. A 65-year-old man presents to the emergency room with blood pressure of 220/120 mm Hg, altered mental status, and seizures. This hypertensive emergency could be caused by which of the following?

- A. Poor adherence to antihypertensive medication
- B. Use of NSAIDs
- C. Alcohol or substance abuse
- D. Underlying pheochromocytoma
- E. All of the above

25-10. A 42-year-old woman in her second trimester of gestation requires antihypertensive therapy for her chronic hypertension. Which of the following is *not* safe to prescribe to her?

- A. ACEI
- B. Methyldopa
- C. Labetalol
- D. Nifedipine
- E. All of the above

ANSWERS

25-1. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 25*) By current guidelines, normal (optimal) pressure is classified as blood pressure < 120/80 mm Hg (option C). Hypertension is highly prevalent in adult populations throughout the world and is increasing in relation to increased overweight and reduced daily exercise (option E), and it is a growing cause of fatal and nonfatal cardiovascular and renal disease worldwide (option A).^{1,2} The benefits of treating hypertension have been firmly established.^{3,4}

The introduction of 24-hour ambulatory blood pressure monitoring and systematic home blood pressure monitoring has brought to light the fact that blood pressure measured outside the office or clinic may differ substantially from office or clinic pressure (option D). The importance of out-of-office blood pressures for accurate prognosis is now supported by several national and international guidelines.⁵⁻⁸

25-2. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 25*) Most hypertensive patients are initially identified during office or clinic visits when seen for checkups or nonemergent symptoms. Initial evaluation and classification of these patients is crucial because hypertension is mostly a silent disorder, and patients are often asymptomatic for long periods of time. The goals for the initial evaluation of hypertensive patients include: estimating the average blood pressure (option A), considering the overall cardiovascular risk status (option B), determining the presence or absence of target organ pathology (option C), and beginning the process of education that will lead the patient to recognize and collaborate in long-term risk reduction (option D). It is also an opportune moment to assess the patient for identifiable (secondary) hypertension. Therefore, all of the above are correct (option E).

25-3. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 25*) Blood pressure measurement in the clinic requires careful

and consistent practice.⁹ Choosing an appropriate cuff size is essential for accurate pressure readings; therefore, larger adult cuffs are mandatory for most large or obese patients (option A). In general, a cuff that is too large will underestimate blood pressure. During measurement, the patient should be seated comfortably, and pressures should be taken in both arms due to possible variability. Blood pressures can also be measured in the standing position (option B) to assess for orthostatic hypotension, particularly in the elderly and in those with dizziness.¹⁰ Brachial artery pressures may fail to reflect central aortic pressures (option E), the latter of which is measured directly by invasive catheterization.

- 25-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 25*) Ambulatory blood pressure measurement is a noninvasive, fully automated technique in which multiple blood pressure measurements are recorded over an extended period (typically 24 hours). It can thus measure blood pressure when a patient is awake during the day, as well as when the patient is sleeping during the night (option E). Studies suggest that the average level of ambulatory blood pressure predicts risk of morbid events better than clinic blood pressure (option A).¹¹ Ambulatory blood pressure monitoring is valuable for determining whether the patient's usual pressure, in "real life," is either higher or lower than the clinic pressure, thereby enabling the diagnosis of both white coat (option B) and masked hypertension (option C). Nevertheless, a careful and well-focused medical history and physical examination are the foundation for the initial appraisal of a hypertensive patient and his or her risk for cardiovascular disease, and these cannot be substituted by the use of this device (option D).
- 25-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 25*) After the initial assessment of hypertensive patients, appropriate follow-up reassessment is crucial. Studies have shown that increased cardiovascular event rates were related to failure to intensify treatment, delays of more than 1.4 months for intensification, and delays in follow-up of more than 2.7 months after intensification.¹² In general, the higher the blood pressure, the greater the need for shorter intervals between revisits. Therefore, while smoking cessation is important for cardiovascular prevention, 1 year is too long an interval for follow-up (option C). There is general agreement that in the absence of clues to identifiable hypertension, efficient use and appropriate selection of laboratory resources can be confined to those needed to define cardiovascular risk, to target organ pathology, and to establish a baseline for treatment (option E). Subsequently, appropriate treatment should focus on lifestyle improvement such as adherence to an adequate diet (option A) and increased exercise (option B), as well as prescription of antihypertensive drugs (option D).
- 25-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 25*) Thiazides have been the mainstay of antihypertensive drug treatment since the 1960s as single agents or in effective two-drug combinations. The most frequent adverse reaction to these drugs is hypokalemia, due to their effect on potassium excretion by the kidneys (option B). Loop-active diuretics are preferred over thiazides when renal function is impaired or in the presence of congestive heart failure, but they share similar adverse reactions, including hypokalemia (option C). Potassium-sparing diuretics, on the other hand, reduce potassium excretion by the kidneys and therefore do not cause hypokalemia (option A). They are valuable for treating primary aldosteronism or thiazide-related hypokalemia.
- 25-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 25*) The effectiveness of beta-receptor blockers for the prevention of cardiovascular disease in the absence of coronary artery disease is uncertain.^{13,14} However, the role of beta-blockers in the management of coronary heart disease, especially angina, remains well accepted.¹⁵ Alpha-blockers may be combined with a beta-blocker for persons with highly variable blood pressure associated with tachycardia (option E). Likewise, ACEIs (option C) and ARBs (option D) can be safely used with beta-receptor blockers as antihypertensive drugs in the context of coronary heart disease. Non-dihydropyridine calcium channel blocker, on the other hand, inhibits cardiac AV conduction and should not be combined with beta-receptor blockers because of the risk of bradycardia (option B).
- 25-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 25*) The prevalence and severity of hypertension are not entirely uniform in comparing populations with different ethnic status, with increased prevalence in non-Hispanic (black) groups.¹⁶ In addition, the treatment rates and drug responses vary across groups (option E). Beta-blockers may mask the symptoms of hypoglycemia ("hypoglycemic unawareness"), while diuretics and ACEIs have no discernable effect (option A).¹⁷ In addition, the coexistence of diabetes and hypertension confers a two- to threefold greater risk of future cardiovascular disease compared to hypertension alone (option B).^{18,19} Antihypertensive drug therapy continues to be important even after a stroke has occurred, as studies have shown that the combination of an ACEI and diuretic is effective for preventing the occurrence of a second stroke (option D).²⁰ Finally, the occurrence of cancer in hypertensive patients is all too frequent, and the incidence of new hypertension or worsening of previous hypertension in cancer patients may result from chemotherapy with the VEGF inhibitors, varying from 20% to 70% (option C).²¹
- 25-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 25*) A hypertensive emergency is defined by a rapid increase in blood pressure linked to an immediate threat to target organs.^{22,23} Although there is no blood pressure threshold for the diagnosis of hypertensive emergencies, most end-organ damage is noted with systolic blood pressures exceeding 220 mm Hg or diastolic blood pressures exceeding 120 mm Hg. The condition is usually related to a rapid increase in pressure from already high levels in established hypertension, perhaps related to poor adherence to antihypertensive medications. However, abrupt increases in pressure with threat to target organs may appear without prior warning as in some patients with pheochromocytoma or some forms of renal disease (eg, scleroderma renal crisis). The medical history should include queries about the use of nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, and substance use.

25-10. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 25*) The goals and strategy for treating hypertension in pregnancy differ from the usual pattern for nonpregnant women.²⁴ For women with treated hypertension before pregnancy, pressure should be kept in the range of 120–160/80–105 mm Hg. However, the range of drug classes suitable for treating hypertension in pregnancy is a restricted one, excluding the renin system blockers such as ACEIs (option A) because of the risk of fetal damage.^{25,26} Recommended drugs are methyldopa (option B), labetalol (option C), and nifedipine (option D) because these have acceptable evidence of safety in pregnancy.

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SECTION 5

Metabolic Disorders and Cardiovascular Disease

CHAPTER 26

The Metabolic Syndrome

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

26-1. Which of the following is *not* considered a component of the metabolic syndrome (MetS)?

- A. Central adiposity
- B. Insulin resistance
- C. High serum low-density lipoprotein (LDL) cholesterol
- D. High serum triglycerides
- E. Hypertension

26-2. Which of the following statements concerning the MetS is *not true*?

- A. Insulin resistance and central adiposity are required for a diagnosis of MetS
- B. Three of the five criteria are always required for a diagnosis of MetS
- C. Between 20% and 35% of the worldwide adult population have MetS
- D. Atherosclerotic risk rises in association with the severity of MetS
- E. Residual risk describes the remaining increased risk for atherosclerosis after the treatment of a specific risk factor

26-3. Which of the following is *not* a mechanism by which physical activity affects metabolism?

- A. Activation of brown fat
- B. Improvement in insulin sensitivity
- C. Modulation of endothelial and adipose tissue function
- D. Gene activation
- E. All of the above are mechanisms by which physical activity affects metabolism

26-4. Which of the following concerning sleep is *true*?

- A. Six hours of sleep per night is sufficient for the average adult
- B. Reduced sleep is associated with hypertension
- C. Sleep quality has no known effects on metabolism
- D. Shift workers do not differ from the general population in rates of obesity
- E. Adults sleep more on average today than 50 years ago

26-5. Which environmental factors could affect the prevalence of MetS?

- A. Modern agricultural practices
- B. Exposure to endocrine-disrupting chemicals
- C. Industrial production of sugars
- D. Antidepressant and antibiotic use
- E. All of the above

26-6. Which of the following is considered the common starting pathway for the development of MetS?

- A. Genetic predisposition
- B. Insulin resistance
- C. Systemic inflammation
- D. Accumulation of fat in adipose or nonadipose tissue
- E. Hypertension

- 26-7.** The presence of which of the following would *not* raise a suspicion of MetS?
- A. Alzheimer's disease
 - B. Polycystic ovary syndrome
 - C. Obstructive sleep apnea
 - D. Gestational diabetes
 - E. Family history of hypertension
- 26-8.** What is the approximate annual risk of developing type 2 diabetes in a patient with obesity and MetS?
- A. 2.5%
 - B. 5%
 - C. 7.5%
 - D. 10%
 - E. 12.5%
- 26-9.** What is the most important factor when selecting a dietary intervention for a patient with MetS?
- A. Minimization of refined carbohydrates
 - B. Avoidance of processed foods
 - C. Consumption of lean meats
 - D. Consumption of large amounts of vegetables and fruits
 - E. Ability to maintain the dietary intervention long-term
- 26-10.** Which of the following procedures is associated with the least improvement in type 2 diabetes?
- A. Roux-en-Y gastric bypass (RYGB)
 - B. Sleeve gastrectomy (SG)
 - C. Laparoscopic gastric banding (LGB)
 - D. Biliopancreatic diversion with duodenal switch
 - E. Biliopancreatic diversion without duodenal switch

ANSWERS

- 26-1. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 26*) The metabolic syndrome is a theoretical construct from the clustering of interrelated processes to better represent complex pathophysiology for actionable and effective clinical decision making. Specifically, the rationale and practical utility of MetS is to facilitate early diagnosis, risk stratification, and management of cardiometabolic risk factors. This topic is relevant, but it also remains controversial because many aspects remain unproven. Nevertheless, the core principle is that the value of MetS is related to the impact of residual risk (total risk minus the aggregate of known specific risk factors) on cardiovascular disease (CVD). Currently, the diagnosis of MetS is based on a set of commonly measured metabolic markers: abdominal girth (option A), hyperglycemia (option B), hypertriglyceridemia (option D), hypertension (option E), and low high-density lipoprotein (HDL) levels. However, debate still exists over the relative weighting of each of these measures in a predictive model for morbidity and mortality risk. Low-density lipoprotein levels are not among the diagnostic criteria (option C).
- 26-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 26*) While the diagnostic criteria for MetS vary by organization, either insulin resistance or central adiposity (but not both) are generally required for a diagnosis of MetS (option A). The exception is the criteria of the American Heart Association/National Heart, Lung, and Blood Institute, which do not make a specific requirement for either. By all definitions, three of five criteria (abdominal girth, hyperglycemia, hypertriglyceridemia, hypertension, and low HDL levels) are required for a diagnosis of MetS (option B). Depending on the specific criteria used, approximately 20% to 35% of various reported worldwide adult populations have MetS (option C). Overall, atherosclerotic risk rises in association with the severity of MetS (option D).^{1,2} The practical decisions of diagnosis and clinical intervention should take into consideration the continuum of risk imposed by MetS. The term *residual risk* complements the concept of the MetS. Specifically, residual risk describes the remaining increased potential for atherosclerotic CVD, after the treatment of a specific risk factor, such as using cholesterol-lowering agents with dyslipidemia (option E).³ Factors that contribute to residual risk include lifestyle factors, such as eating patterns and nutrient content, endocrine-disrupting compounds (EDCs), physical activity, sleep hygiene, and others.
- 26-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 26*) Physical activity has multiple effects on metabolism, including the activation of brown fat (option A), improvement in insulin sensitivity (option B), and modulation of endothelial function and adipose tissue function (option C).^{4,5} Shifts in internal energy use among highly active people may also contribute to more efficient carbohydrate processing and reduced insulin resistance.⁶ Additionally, gene

activation following physical activity can influence insulin resistance and mitochondrial function (option D).⁷ Interventional studies consistently demonstrate a great reduction in the prevalence and severity of MetS among highly active subjects.¹ Most notably, trials that incorporate increased physical activity demonstrate a 29% to 58% reduction in the incidence of type 2 diabetes among at-risk subjects.⁸

- 26-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 26*) Many studies demonstrate that a reduced amount of sleep, generally 6 hours or less per night (option A), is associated with increased insulin resistance, hypertension (option B), and obesity.⁹ One large study demonstrated that reduced time of slow-wave sleep was specifically associated with increased waist circumference.¹⁰ Quality of sleep can also affect metabolism (option C). Shift workers with frequent changes in circadian patterns have higher rates of obesity and type 2 diabetes compared to the general population (option D). Insulin resistance also worsens in the presence of obstructive sleep apnea. Current trends over the past 50 years demonstrate a 1.5- to 2-hour reduction in time spent sleeping each night, which may further contribute to the rising prevalence of MetS (option E).¹¹
- 26-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 26*) The potential adverse metabolic effects of modern agricultural techniques (option A), food processing, and the resultant food chain in the United States with respect to nutrient content and endocrine disruptors are only just becoming clear, but they are still not without controversy. For example, the use of corn for animal feed rather than grass for beef production or seeds for poultry yields a higher n-6 fatty acid content, which may have proinflammatory effects.¹² A number of man-made industrial chemicals have properties that can interrupt normal hormone signaling either through molecular mimicry of natural hormones, blockade of hormone activity, or by affecting hormonal synthesis, transport, binding, or catabolism (option B). Animal models and population exposure studies identify specific endocrine-disrupting chemicals, such as pesticides, plasticizers, preservatives, and artificial sweeteners, among other chemicals that hinder glucose metabolism and cause insulin resistance.¹³⁻¹⁶ However, the degree to which endocrine-disrupting chemicals (EDCs) contribute to the high prevalence of MetS is unclear. The high content of fructose within industrially produced sugars (option C), such as sucrose and high-fructose corn syrup, makes this inefficiently metabolized monosaccharide highly available. Multiple longitudinal and cross-sectional studies demonstrate a strong association among high fructose intake and the development of obesity, MetS, and/or vascular disease.¹⁷⁻²⁰ The rising use of certain antidepressant and other psychotropic medications (option D) that affect metabolic control within the hypothalamus leads to insulin resistance and weight gain. Even the widespread use of antibiotics may influence metabolism through the alteration of intestinal microbiota (option D).²¹ The average American adult is given one to two prescriptions for antibiotics annually, which has been associated with the development of obesity.²¹ Macrolides confer the greatest risk, perhaps reflecting a greater effect on intestinal microbiota.^{21,22}
- 26-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 26*) It is useful to view a common starting pathway for the MetS as the accumulation of fat in adipose or nonadipose tissue (option D), which increases systemic inflammation (option C) and insulin resistance (option B). Pancreatic β -cell dysfunction ensues via degeneration or transformation to inactive cells.²³ Impaired insulin signaling leads to further accumulation of fat mass.²⁴ Reduced release and reduced activity of glucagon-like peptide-1 (GLP-1) by L-cells of the distal ileum worsens insulin resistance and drives further increases in adipose tissue.²⁵ Nutrient sensing within the paraventricular nucleus of the hypothalamus becomes impaired, and resistance to leptin develops within the arcuate nucleus.²⁶ Adiponectin production within adipose tissue is also diminished, which further promotes insulin resistance.²⁷ Insulin resistance reduces endothelial and adipose lipoprotein lipase activity, yielding small, dense LDL particles that enter the circulation and are highly atherogenic.²⁸ Circulating free fatty acids further drive insulin resistance through oxidative stress and accumulation of intracellular derivatives such as ceramides.²⁹ Visceral fat stores increase, leading to hepatosteatosis and fat accumulation within the pancreas, promoting insulin resistance and β -cell dysfunction.^{30,31} Within the vascular endothelium, insulin resistance also impairs nitric oxide (NO) synthase activity, which diminishes NO production, affecting vasodilation and leading to the development of essential hypertension (option E).³² Low circulating adiponectin and resistance to leptin induce increased expression of endothelin-1, further driving vasoconstriction and promoting hypertension.³² High levels of circulating lipid particles naturally oxidize and are taken up by macrophages that become activated.³³ Free fatty acids also bind toll-like receptor 4 on macrophage cell surfaces.³⁴ Both processes trigger the release of inflammatory cytokines such as tumor necrosis factor- α (TNF α), interleukin (IL)-1, and IL-6. These cytokines promote the degradation of insulin receptor substrate-1, a downstream mediator of insulin activity, further driving insulin resistance.³³ Very few genes have been identified that specifically confer a risk of MetS (option A).³⁵ However, epigenetic phenomena secondary to behavioral and environmental factors do have great potential to influence the development of obesity and MetS.
- 26-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 26*) The high prevalence of MetS should trigger aggressive case finding in a large portion of the general population.³⁶ Signs of obesity, weight gain, hypertension, hyperlipidemia, and hyperglycemia can be early markers of MetS. People with a family history of type 2 diabetes, hypertension (option E), and CVD should also be evaluated for MetS. Additionally, the presence of other conditions associated with insulin resistance, such as polycystic ovary syndrome (option B), hepatosteatosis, obstructive sleep apnea (option C), or gestational diabetes (option D), should raise suspicion for MetS. Diagnosing a person with MetS emphasizes the decision to intervene.

- 26-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 26*) The annual risk of type 2 diabetes (T2D) is approximately 2.5% when stratified by fasting glucose (option A).³⁷ In people with obesity and MetS, the annual risk of T2D is nearly 5% (option B), although annual regression of hyperglycemia is about 10%, emphasizing the need for intensive lifestyle changes as part of a preventive care paradigm.³⁷ By virtue of its syndromic nature, this preventive care approach to people at high risk for MetS should follow the same treatment strategies for MetS. The intensity of intervention should parallel the severity of each MetS component.³⁶ A striking theme among the major clinical trials investigating individual criteria of MetS is that early, intensive intervention is best at reducing adverse outcomes, especially with the intention of atherosclerotic risk reduction.^{8,38-42}
- 26-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 26*) In early MetS, when the severity of component risks is mild, lifestyle interventions should be implemented that minimize refined carbohydrates (option A), avoid processed foods (option B), favor meats that are lean (option C), and contain large amounts of fruits, vegetables, and fish (option D). Debate continues over the ideal diet, but beneficial dietary pattern examples include the Mediterranean diet, the New Nordic diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Ornish diet. The use of very low carbohydrate diets, such as the Atkins diet, can also be considered. The most important consideration for dietary intervention is the person's ability to maintain this new lifestyle over the long term (option E).⁴³
- 26-10. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 26*) Approved bariatric surgical procedures include the RYGB (option A), SG (option B), biliopancreatic diversion with or without duodenal switch (BPD) (options D and E), and LGB (option C). Surgically induced changes in the gastrointestinal tract affect energy physiology, insulin resistance, hypertension, hyperlipidemia, and other weight-related complications.⁴⁴ Additionally, many of the factors contributing to MetS improve, and the risk of cardiovascular events and mortality is reduced.⁴⁵ In people undergoing RYGB, SG, or BPD, insulin resistance improves in the immediate postoperative period, signifying the predominance of improved energy regulatory hormone signaling well before weight loss occurs.⁴⁶ Following LGB, insulin resistance declines in association with weight loss.⁴⁶ The significant improvement and possible resolution of T2D is also substantially higher following RYGB, SG, and BPD, when compared to LGB.⁴⁷⁻⁴⁹ These observations suggest that the metabolic benefits of RYGB, SG, and BPD may confer additional improvement to people with MetS.

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CHAPTER 27

Obesity and Cardiovascular Disease

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 27-1.** What approximate proportion of the adult population worldwide is overweight or obese?
- A. 20%
 - B. 30%
 - C. 40%
 - D. 50%
 - E. 60%
- 27-2.** What proportion of a person's risk for obesity is attributable to genetic factors?
- A. < 10%
 - B. 10% to 20%
 - C. 30% to 40%
 - D. 50% to 60%
 - E. > 60%
- 27-3.** Which of the following does *not* occur in response to weight loss?
- A. Increased secretion of ghrelin
 - B. Increased secretion of leptin, cholecystokinin, glucagon-like peptide-1, amylin, and peptide YY
 - C. Decreased resting energy expenditure
 - D. Increased hunger
 - E. Increased calorie-dense food preferences
- 27-4.** What proportion of body weight must be lost to achieve predictable therapeutic benefits for obstructive sleep apnea?
- A. 2.5%
 - B. 5%
 - C. 7.5%
 - D. 10%
 - E. 12.5%
- 27-5.** Which of the following is *not true* concerning body mass index (BMI)?
- A. National Institutes of Health obesity-defined BMI is divided into three classes: obese class I (BMI 30–34.9), obese class II (BMI 35–39.9), and obese class III (BMI \geq 40)
 - B. Cutoff values for classifying individuals as underweight, normal, overweight, or obese vary by population
 - C. BMI will overestimate adiposity in athletes with high muscle mass
 - D. BMI is a significant independent predictor of cardiovascular disease (CVD)
 - E. In patients with congestive heart failure, overweight and obesity are protective against mortality
- 27-6.** Which of the following statements concerning the clinical component of the diagnosis of obesity is *not true*?
- A. Individuals who meet the anthropometric criterion for overweight or obesity should undergo a clinical evaluation for weight-related complications
 - B. In many cases, information gathered in the initial examination is sufficient for the diagnosis of certain weight-related complications
 - C. The goal of weight-loss therapy is to treat and prevent weight-related complications

- D. Even metabolically healthy obese patients should be treated aggressively to reduce risk for coronary heart disease
- E. BMI does not indicate the impact of excess adiposity on the health of individual patients

27-7. Which of the following is *not true* about the effects of weight loss on CVD risk factors?

- A. Weight loss is the most effective therapeutic approach for treating and preventing the progression of cardiometabolic disease
- B. If weight loss is not sustained over time, its beneficial effect on type 2 diabetes incidence is lost
- C. Weight loss is an effective approach for reducing blood pressure
- D. Weight loss decreases triglycerides and LDL, while increasing HDL
- E. Weight loss has beneficial effects on LDL subclasses characterized by reductions in small, dense LDL particle concentrations and an increase in medium and large LDL particles

27-8. Which of the following is *not* appropriate for staging cardiometabolic risk in insulin resistant patients?

- A. American College of Cardiology/American Heart Association Omnibus risk estimator
- B. Framingham Coronary Heart Disease Risk Score
- C. Reynolds Risk Score
- D. Cardiometabolic Disease Staging System
- E. American Heart Association/National Heart, Lung, and Blood Institute diagnostic criteria for metabolic syndrome (MetS)

27-9. Which of the following weight-loss medications is approved for the treatment of obese adolescents?

- A. Orlistat
- B. Lorcaserin
- C. Phentermine/topiramate
- D. Naltrexone/bupropion
- E. None of the above

27-10. In which of the following patient group(s) could bariatric surgery be considered?

- A. BMI of 35 kg/m² or more
- B. BMI of 35 kg/m² or more with at least one associated comorbidity
- C. BMI of 40 kg/m² or more
- D. Both B and C
- E. A, B, and C

ANSWERS

27-1. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 27*) Prevalence rates of obesity have increased sharply worldwide over the past 30 years.¹ Worldwide, the proportion of adults with a BMI of 25 kg/m² or greater increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women.² Prevalence has increased substantially in children and adolescents in developed countries, to the point where 23.8% of boys and 22.6% of girls were overweight or obese in 2013.² In the United States, data from the National Health and Nutrition Examination Survey (NHANES) show that roughly two out of three US adults are overweight or obese, more than one-third are obese, and 17% of children are obese.^{3,4} This has created a global health crisis with a profound impact on morbidity, mortality, and health care costs largely attributable to weight-related complications.

27-2. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 27*) Like many other chronic diseases, genetic factors constitute a substantial component of disease risk⁵ that can explain 50% to 60% of individual variation in body weight in monozygotic/dizygotic twin studies. Monogenic forms of the disease are rare, such as in families with leptin or leptin receptor mutations or deletion of the *SNORD116* gene cluster in patients with Prader–Willi syndrome. Susceptibility to obesity in most people results from the inheritance of multiple genes, with each allele conferring a very small relative risk for the disease. Genomewide association studies have identified more than 100 susceptibility loci for obesity.⁶ Particularly strong association signals have been detected for the fat mass- and obesity-associated gene (*FTO*) and the melanocortin-4 receptor (*MC4R*) gene, but even these variants confer odds for obesity of less than 1.7.^{7,8} The multiple susceptibility genes interact with each other and with the environment, behavior, and biological factors to produce individual variation in the risks of obesity. The development of excess adiposity is a complex process; however, those individuals who inherit larger subsets of obesity susceptibility genes will tend to be more overweight in any given environment.^{9,10} Progressive weight gain is not a lifestyle choice and cannot be viewed in terms of a simple thermodynamic equation of greater energy in than energy out. Rather, gene-environment interactions generate a human biological and behavioral interface unique to each person that not only determines body weight but also explains

individual variation in the net effect on body weight for any given amount of food intake or physical activity.

- 27-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Homeostatic dysregulation in the hypothalamus adversely affects appetite and satiety as they respond to peripheral hormones that register fuel storage and availability. With obesity, these mechanisms drive an increase in appetite, producing a positive energy balance, which generates and maintains a higher body weight.^{11,12} Following a weight-loss intervention, secretion of ghrelin from the stomach is increased above baseline both before and after meals (option A). Ghrelin stimulates neuropeptide Y (NPY) and Agouti-related peptide neurons in the arcuate nucleus of the hypothalamus, causing the release of NPY, which activates orexigenic neural pathways, leading to an increase in appetite (option D). At the same time, hormones from the gastrointestinal tract and pancreas (eg, leptin, cholecystokinin, glucagon-like peptide-1, amylin, and peptide YY) are reduced below baseline levels (option B).¹² These latter hormones circulate to the hypothalamus and stimulate proopiomelanocortin-expressing neurons in the arcuate nucleus to produce α -melanocyte-stimulating hormone (MSH). The α -MSH binds upstream MC4R receptors to activate anorexigenic neural pathways, resulting in suppression of appetite. The fall in these satiety-producing hormones has an additional effect to stimulate appetite. Furthermore, in response to weight loss, resting energy expenditure rates are decreased (option C), and the energy that muscles use for any given amount of work is also decreased (ie, increased muscle energy efficiency). These energetic changes also promote weight regain.¹³ Finally, psychological food preferences become oriented to foods of greater caloric density with high fat and sugar content (option E).
- 27-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Obesity markedly augments the risk of obstructive sleep apnea, which interrupts normal sleep with periods of hypoxia. This establishes a vicious cycle whereby progressive weight gain exacerbates sleep apnea and sleep apnea promotes further weight gain.^{14,15} Obstructive sleep apnea adversely affects psychological health, causing fatigue and depression, affects metabolic health by predisposing to MetS and type 2 diabetes, and affects cardiovascular health as an independent risk factor for refractory hypertension, stroke, and CVD.¹⁶⁻²⁰ The therapeutic options for obstructive sleep apnea include continuous positive airway pressure therapy and weight loss.^{21,22} The severity of sleep apnea is quantified by the apnea-hypopnea index (AHI), which reflects the average number of apneic/hypopneic episodes per hour during a polysomnography study.²³ Weight loss, whether achieved by lifestyle therapy²² or obesity medications,²² can dramatically improve both AHI scores and symptomatology; however, therapeutic benefits are most predictably achieved with at least 10% weight loss.^{21,22}
- 27-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 27*) The criteria established by the World Health Organization in 1998²⁴ defines that BMI values 18.5 to 24.9 kg/m² are indicative of lean individuals, BMIs 25 to 29.9 kg/m² overweight, and BMIs of 30 kg/m² or more represent obesity categorized as obese class I (BMI 30–34.9), obese class II (BMI 35–39.9), or obese class III (BMI \geq 40) (option A). These criteria were soon thereafter adopted by the National Institutes of Health.²⁵ However, in South Asian, East Asian, and Southeast Asian populations, health is adversely affected at lower levels of BMIs, and alternate criteria have been advocated, with BMIs of 18.5 to 22.9 kg/m² indicative of normal weight, 23 to 24.9 kg/m² overweight, and 25 or more kg/m² obese (option B).²⁶ BMI is an anthropometric measure that interrelates the height and weight of individuals, and, therefore, is only an indirect measure of adiposity of total body fat mass. BMI incorporates lean mass, fat mass, bone mass, and fluid status, all of which can vary independently from fat mass. BMI will overestimate adiposity in athletes with high muscle mass (option C) and in patients with edema and will underestimate adiposity in elderly patients with sarcopenia. For this reason, patients with elevated BMI measurements must be clinically evaluated to confirm excess adiposity. It is important to consider that the association between BMI and CVD is largely explained by its association with other risk factors, such that independent risk conferred by BMI is usually minimized in multivariate analyses (option D). For example, when adjusted for waist circumference or the presence of MetS, BMI is no longer a significant independent risk factor for CVD or becomes a much weaker predictor.²⁷⁻³¹ Regarding congestive heart failure (CHF), the presence of overweight or obesity may be protective against mortality, referred to as the *obesity paradox* (option E). Elevations in BMI are associated with increased risk of developing CHF in part by predisposing to hypertension, type 2 diabetes, sleep apnea, and CVD. However, once patients present with CHF, the presence of overweight and/or obesity has been observed to be protective regarding risks of future CVD mortality and hospitalizations when compared with lean individuals.³²⁻³⁴ Better outcomes in overweight or obese subjects may reflect reverse causality resulting from processes that both lower body weight and increase mortality (eg, cardiac cachexia and cigarettes).
- 27-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Body mass index status as lean, overweight, or obese does not substantially affect coronary heart disease risk in metabolically healthy patients (those with no other MetS traits), so aggressive weight-loss treatment would not be expected to reduce the risk for coronary heart disease in these patients (option D). Metabolically healthy obese individuals exhibit relatively low rates of future type 2 diabetes, cardiovascular events, and mortality.^{27,35-38} BMI does not indicate the impact of excess adiposity on the health of individual patients (option E).³⁹ Therefore, individuals who meet the anthropometric criterion for overweight or obesity must then undergo a clinical evaluation for the presence or absence of weight-related complications (option A).^{39,40} The presence and severity of complications or relevant risk factors will indicate the need for more aggressive therapy to improve the health of individual patients. The identification of complications does not involve an extensive or extraordinary degree of testing but can be ascertained in the course of an initial patient evaluation consisting of medical history, review of systems, physical examination, and laboratory studies. In many cases, the information gathered in the initial examination

is sufficient for the diagnosis of certain weight-related complications (option B). For other complications, the initial information augments the degree of suspicion, and additional testing consistent with standards of care is then needed to confirm the diagnosis and to stage the severity of the complication. The goals of weight-loss therapy are to improve the health of patients with obesity by treating and preventing weight-related complications (option C).

- 27-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Weight loss is perhaps the most effective therapeutic approach for treating and preventing the progression of cardiometabolic disease (option A) via improvements in the core physiological processes that confer risk of future type 2 diabetes (T2D) and CVD events. Three major randomized clinical trials, the Diabetes Prevention Program,⁴¹ the Finnish Diabetes Study,⁴² and the Da Qing Study,⁴³ all demonstrated the impressive efficacy of lifestyle/behavioral therapy to prevent T2D. With observational follow-up after termination of the Diabetes Prevention Program study, there was still a significant reduction in the cumulative incidence of T2D in the lifestyle treatment group at 10 years, despite the fact that BMI levels had equalized among the three treatment arms (option B).⁴¹ Hypertension is an established consequence of overweight and obesity. It is therefore not surprising that one of the associated benefits of weight reduction is lowering blood pressure (option C). A meta-analysis suggests that blood pressure decreases by 1.2/1.0 mm Hg for every kilogram of weight lost. Weight loss of 5% to 10% has been shown to amplify the benefits of changes in macronutrient composition, resulting in a 20% decrease in triglycerides, a 15% reduction in LDL cholesterol, and an 8% to 10% increase in HDL cholesterol (option D). However, greater degrees of weight loss can achieve progressive improvements in dyslipidemia. Meta-analyses have reported that for every kilogram of weight loss, triglyceride levels decrease about 1.9% or 1.5 mg/dL.⁴⁴ Furthermore, there are beneficial effects of weight loss on LDL subclasses characterized by reductions in small, dense LDL particle concentrations and an increase in medium and large LDL particles, coupled to a mean increase in LDL particle size and reductions in total LDL particle concentration (option E).^{44,45}
- 27-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Estimates of cardiometabolic disease risk can be used to identify patients at greatest risk for future type 2 diabetes (T2D) and CVD in order to target more aggressive weight-loss therapy to those individuals who will receive the greatest benefit. The clinician should evaluate patients for MetS and prediabetes, because this effectively identifies individuals at high risk for future T2D and CVD. However, MetS and prediabetes have high specificity but low sensitivity for identifying patients with insulin resistance and cardiometabolic disease,^{37,46} and these entities alone will not identify significant proportions of at-risk patients (option E). Various indices using information from history and physical examination, such as the American College of Cardiology (ACC)/American Heart Association (AHA) Omnibus risk estimator (option A),⁴⁷ Framingham Coronary Heart Disease Risk Score (option B),⁴⁸ the Reynolds Risk Score (option C),⁴⁹ or commercial products that use clinical laboratory assays, can be used to stage risk in insulin-resistant patients whether or not they meet diagnostic criteria for MetS or prediabetes. Another approach to cardiometabolic disease risk stratification for the patient with obesity is the Cardiometabolic Disease Staging system (CMDS) (option D).^{27,28} CMDS defines five stages of risk that are based on established physiological and epidemiological observations to quantitatively stratify the risk of both T2D and CVD.
- 27-9. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Orlistat (option A) is the only approved long-term drug for obese adolescents aged at least 12 years, while all others (options B, C, and D) are only approved for adult patients. Since 2012, there have been four new weight-loss medications approved for the chronic treatment of obesity by the FDA.^{50,41,51,52} These medications are in addition to orlistat (120 mg), approved in 1999, which was the only preexisting medication for long-term pharmacotherapy and the only one currently permitted in Europe and many other countries. The newer medications include lorcaserin, phentermine/topiramate extended-release (ER), naltrexone ER/bupropion ER, and high-dose liraglutide (3 mg). The availability of these new medications has greatly expanded treatment options for patients with obesity and has led to more robust approaches to patient management.⁴⁰ All these medications are approved in the United States as adjuncts to lifestyle modification in overweight patients with BMIs of 27 to 29.9 kg/m² having at least one weight-related comorbidity (generally taken to be diabetes, hypertension, or dyslipidemia), or obese patients (BMI ≥ 30 kg/m²) whether or not comorbidities are present.
- 27-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 27*) Bariatric surgery is the most effective method for treating class II and III obesity^{53,54} and can be considered in patients with (1) BMIs of 35 kg/m² or more and associated comorbidities (option B) or (2) BMIs of 40 kg/m² whether or not accompanied by comorbidities, particularly after failure of lifestyle modification and medical therapies (option C). Bariatric surgery can provide substantial weight loss (15% to more than 40%), but this varies by procedure.⁵⁴ The most commonly performed procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding, sleeve gastrectomy, and biliopancreatic diversion with or without duodenal switch. Many patients achieve long-term weight loss; however, it is not uncommon for patients to gradually regain weight over time.⁵⁵ Sustained weight loss also depends on ongoing lifestyle therapy, patient reeducation in terms of active lifestyle changes, and long-term medical follow-up.

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CHAPTER 28

Diabetes and Cardiovascular Disease

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

28-1. A 41-year-old woman with a history of atrial fibrillation presents to your office. Which of the following is *incorrect*?

- A. A normal glycated hemoglobin should be < 6.0%, while a glycated hemoglobin of 6.0% to 6.5% is considered prediabetes
- B. A glycated hemoglobin level of 6.5% or higher on two separate occasions indicates diabetes
- C. Prediabetes can be diagnosed by a fasting plasma glucose of 100 mg/dL or more (impaired fasting glucose), a postglucose load of 140 to 199 mg/dL (impaired glucose tolerance), or both
- D. Diabetes can be diagnosed by a fasting plasma glucose > 126 mg/dL or a 2-hour postprandial glucose of > 200 mg/dL during an oral glucose tolerance test involving a glucose solution containing the equivalent of 75 grams of glucose dissolved in water
- E. Diabetes can be diagnosed in the patient who has a random plasma glucose of > 200 mg/dL with classic symptoms of hyperglycemia

28-2. An obese 17-year-old woman now present with her second pregnancy. Which of the following is *incorrect*?

- A. Patients who are overweight or obese with a body mass index (BMI) of > 25 kg/m² or in the case of Asian Americans of 23 kg/m² or higher should be screened for diabetes
- B. Children and adolescents who are overweight or obese should be screened for diabetes
- C. With regard to gestational diabetes, patients with risk factors should be tested in the first prenatal visit. At 28 weeks' of gestation, pregnant women who are not previously known to have diabetes should be tested for gestational diabetes
- D. Women with a history of gestational diabetes are considered to have prediabetes and should receive lifestyle interventions for the prevention of diabetes
- E. All are correct

28-3. Which of the following is *incorrect*?

- A. In 1985, an estimated 30 million people worldwide had diabetes
- B. It is expected that there will be 350 million people worldwide with diabetes by 2025
- C. In the United States in 2012, the unadjusted prevalence of diabetes was 19.3% (95% confidence interval [CI], 7.8%–11.1%)
- D. Within the diabetes population, 25.2% (95% CI, 21.1%–29.8%) were undiagnosed
- E. All are correct

28-4. A 70-year-old man with a history of diabetes, coronary artery disease (CAD), and hypertension has now developed diabetic nephropathy. Which of the following should *not* be used when treating this patient?

- A. Control of hypertension with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
- B. Glycemic control
- C. Sodium restriction
- D. Adjustment of protein intake
- E. Renal arteriography if systolic blood pressure is > 170 mm Hg despite treatment with two antihypertensive agents

28-5. Which of the following statements is *not true* regarding type 2 diabetes mellitus and coronary heart disease?

- A. Coronary heart disease (CHD) is strongly associated with type 2 diabetes mellitus and is the leading cause of death regardless of the duration of disease
- B. There is a two- to fourfold increase in the relative risk ratio of cardiovascular disease in type 2 diabetes patients compared to the general population. This increase is particularly disproportionate in diabetic women when compared with diabetic

men

- C. The protection that premenopausal women have against CHD is not seen if they suffer from diabetes
- D. The degree of hyperglycemia and the duration of hyperglycemia are strong risk factors for the development of microvascular but not macrovascular complications
- E. Even impaired glucose tolerance increases cardiovascular risk, although there is minimal hyperglycemia

28-6. Which of the following statements is *not true* regarding insulin resistance?

- A. The insulin resistance syndrome is a composite of dyslipidemia, hypertension, hypercoagulability, and microalbuminuria
- B. Insulin resistance is the predominant defect in > 90% of type 2 diabetes patients and the major pathologic mechanism for the susceptibility to premature cardiovascular disease
- C. Hyperinsulinemia is an independent risk factor when adjusted for lipid profile, hypertension, and family history
- D. Studies of multiple ethnic groups show increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance
- E. Because insulin resistance precedes clinically diagnosed type 2 diabetes by 10 to 15 years in as many as 90% of patients, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics

28-7. One of your patients who has a history of diabetes and multivessel percutaneous coronary intervention (PCI) has a glycated hemoglobin of 7.0%. With respect to intensive (< 7.0% glycated hemoglobin) versus usual care strategies for the treatment of diabetes, meta-analyses of clinical trial results indicate which of the following?

- A. For cardiovascular death, there is no difference between the intensive (< 7.0% glycated hemoglobin) and usual care strategies
- B. In long-term studies that combine UKPDS, ACCORD, and VADT, myocardial infarction (MI) was reduced by about approximately 15% over the long term
- C. Apart from a modest reduction in MI rates, there is no significant benefit of a more intensive lowering of glycated hemoglobin with regard to cardiovascular macrovascular end points
- D. One meta-analysis of 27,000 participants with 2370 major cardiovascular events, including hospitalization or death from heart failure, showed no important differences between the more intensive arm compared to the less intensive arm
- E. All of the above are true

28-8. Which of the following statements is *not true* about the treatment of diabetic patients with statins?

- A. For patients with diabetes and known cardiovascular disease, high-intensity statin therapy is recommended according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines of 2013
- B. For patients with diabetes under the age of 40 with one additional cardiovascular risk factor or those age 40 to 75 without any cardiovascular risk factors, moderate to high-intensity statins are recommended
- C. Much of the evidence for the treatment of diabetics with statins comes from subgroup analyses from large randomized trials of lipid-lowering therapies in which diabetic patients represented < 10% of all the patients enrolled
- D. In the trials of statin therapy with hyperlipidemia, the relative benefit appears to be increased among diabetic patients compared with nondiabetic patients
- E. In a pooled analysis from the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering) trials, patients with prediabetes treated with high-intensity compared to low-intensity statins were more likely to develop new onset diabetes over 5 years

28-9. A 45-year-old man with diabetes and palpitations presents to your clinic. Which of the following statements regarding antiplatelet therapy in patients with diabetes is *false*?

- A. For men over age 50 and women over age 60 with at least one additional major cardiovascular risk factor, it is recommended that aspirin therapy at 81 mg daily be instituted as a primary prevention strategy for type 1 and type 2 diabetic patients
- B. For men over age 50 and women over age 60 with at least one additional major cardiovascular risk factor, clopidogrel can be considered as an alternative to aspirin as a primary prevention strategy for type 1 and type 2 diabetic patients
- C. For patients who are under age 50 for men and 60 for women with no additional major risk factors, aspirin therapy is not recommended
- D. For diabetic patients with acute coronary syndromes, the evidence suggests that there is no heterogeneity in the response to newer antiplatelet agents and strategies based on diabetes status
- E. Clopidogrel is associated with a lower bleeding risk than are prasugrel and ticagrelor

28-10. An asymptomatic 65-year-old man with diabetes is referred to you for screening. With respect to screening for coronary artery disease (CAD) in patients with diabetes, which of the following statements is *true*?

- A. Exercise testing in diabetic patients is more likely to be accurate when combined with echocardiography or radionuclide imaging
- B. Diabetic patients are less likely to have an appropriate blood pressure and heart rate response to exercise and less likely to experience any pain corresponding to ST-segment changes caused in part by autonomic dysfunction
- C. The AHA recommends that the finding of subclinical CAD should prompt clinicians to initiate more aggressive

- preventive measures
- D. The DIAD study has shown that the prevalence of silent ischemia in the diabetic population is not insignificant, but the annual cardiac event rate is $< 1\%$ overall at 4.8 years of follow-up, and routine screening for inducible coronary ischemia did not reduce cardiovascular events
- E. All of the above are correct

ANSWERS

- 28-1. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 28*) The universally recognized criteria for the diagnosis of prediabetes and diabetes are as follows: (1) a normal glycated hemoglobin should be $< 5.7\%$, (2) a glycated hemoglobin of 5.7% to 6.4% is considered prediabetes, and (3) a level of 6.5% or higher on two separate occasions indicates diabetes (option B).¹ Prediabetes can be diagnosed by a fasting plasma glucose of 100 mg/dL or more (impaired fasting glucose), a postglucose load of 140 to 199 mg/dL (impaired glucose tolerance), or both (option C). Other recognized criteria include a fasting plasma glucose $> 126\text{ mg/dL}$ or a 2-hour postprandial glucose of $> 200\text{ mg/dL}$ during an oral glucose tolerance test involving a glucose solution containing the equivalent of 75 grams of glucose dissolved in water (option D). Diabetes can also be diagnosed in the patient who has a random plasma glucose of $> 200\text{ mg/dL}$ with classic symptoms of hyperglycemia (option E).
- 28-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 28*) New recommendations identify patients who are at increased risk for diabetes and who require testing. These include patients who were overweight or obese with a body mass index (BMI) of $> 25\text{ kg/m}^2$ or in the case of Asian Americans of 23 kg/m^2 or higher (option A). Recommendations for screening for diabetes have now expanded to screening of children and adolescents who are overweight or obese (option B). With regard to gestational diabetes, patients are tested in the first prenatal visit with risk factors. At 28 weeks' of gestation, there is a test for gestational diabetes in pregnant women who are not previously known to have diabetes (option C). It is recommended that women with a history of gestational diabetes are considered to have prediabetes and should receive lifestyle interventions for the prevention of diabetes (option D).
- 28-3. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 28*) The number of people with diabetes has increased alarmingly since 1985, and the rate of new cases is escalating. In 1985, an estimated 30 million people worldwide had diabetes (option A), and this figure is expected to rise to almost 350 million by 2025 (option B).² In the United States in 2012, the unadjusted prevalence of diabetes was 12.3% (95% confidence interval [CI], 10.8% – 14.1%) (option C). Within the diabetes population, 25.2% (95% CI, 21.1% – 29.8%) were undiagnosed (option D).³
- 28-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 28*) There is insufficient evidence to recommend angiotensin-converting enzyme (ACE) inhibitors in normotensive patients without microalbuminuria. Nonetheless, physicians should still recommend screening on at least a yearly basis, because the risk-to-benefit ratio of diagnosing microalbuminuria justifies treatment with an ACE inhibitor, if not for renal disease alone, then for reducing the incidence of myocardial infarction (MI) (option A). Clinical trials evaluating angiotensin receptor blockers (ARBs), including losartan and irbesartan, have demonstrated a significant renal protective effect in the diabetic patient with nephropathy (option A). There were no differences between the ARB and usual care groups with regard to cardiovascular outcomes.⁴ An optimal approach toward diabetic nephropathy combines control of hypertension, preferably with an ACE inhibitor or ARB, glycemic control (option B), sodium restriction (option C), and adjustment of protein intake (option D). If increasing macroalbuminuria occurs or if renal insufficiency is progressive despite these measures, the patient should be referred to a nephrologist. It is strongly recommended that renal arteriography be avoided (option E). Dietary protein restriction in patients who have progressive renal insufficiency will reduce the accumulation of nitrogen-containing waste products and can have a beneficial influence on the progression of renal insufficiency.
- 28-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 28*) Coronary heart disease (CHD) is strongly associated with type 2 diabetes mellitus and is the leading cause of death regardless of the duration of disease (option A). There is a two- to fourfold increase in the relative risk ratio of cardiovascular disease in type 2 diabetes patients compared to the general population. This increase is particularly disproportionate in diabetic women when compared with diabetic men (option B). The protection that premenopausal women have against CHD is not seen if they suffer from diabetes (option C). The degree of hyperglycemia and the duration of hyperglycemia are strong risk factors for the development of *both* microvascular and macrovascular complications (option D). Even impaired glucose tolerance increases cardiovascular risk, although there is minimal hyperglycemia (option E).⁵
- 28-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 28*) The insulin resistance syndrome is a composite of dyslipidemia, hypertension, and hypercoagulability (option A).⁶ The syndrome composite does not require microalbuminuria. It is only now being recognized that insulin resistance is the predominant defect in more than 90% of type 2 diabetes patients and the major pathologic mechanism for the susceptibility to premature cardiovascular disease (option B). Insulin resistance and hyperinsulinemia accelerate the development of atherosclerosis. Hyperinsulinemia is an independent risk factor when adjusted for lipid profile, hypertension, and family history (option C). Studies of

multiple ethnic groups show increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance (option D). Impaired glucose tolerance can increase the risk of heart disease. Because insulin resistance precedes clinically diagnosed type 2 diabetes by 10 to 15 years in as many as 90% of patients, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics (option E).^{7,8}

28-7. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 28*) Evidence from updated meta-analyses indicates that, for cardiovascular death, there is no difference between the intensive (< 7.0% glycated hemoglobin) and usual care strategies (option A).⁹ In long-term studies that combine UKPDS, ACCORD, and VADT, myocardial infarction (MI) was reduced by about 15% over the long term (option B). Apart from this modest reduction in MI rates, there was no significant benefit of a more intensive lowering of glycated hemoglobin with regard to cardiovascular macrovascular end points (option C). One meta-analysis of 27,000 participants with 2370 major cardiovascular events, including hospitalization or death from heart failure, showed no important differences between the more intensive arm compared to the less intensive arm (option D).¹⁰

28-8. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 28*) Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors—statins—are the frontline therapy in lowering LDL cholesterol levels in type 2 diabetes patients without having an adverse effect on glycemic control. Important evidence from large randomized trials of lipid-lowering therapies is based on subgroup analyses in which diabetic patients represented < 10% of all the patients enrolled (option C); however, more recently studies have been done exclusively in diabetic patients. In the Cholesterol and Recurrent Events (CARE) Trial, which compared pravastatin with a placebo in secondary prevention, the baseline mean LDL concentration in diabetic patients was 136 mg/dL. LDL was reduced 27% in the group receiving pravastatin, which translated into a 25% reduction in coronary events over 5 years compared with the control group.¹¹ The Heart Protection Study (HPS), with a subgroup of 5963 diabetic patients, showed a 28% reduction in total coronary heart disease (CHD), including nonfatal myocardial infarction and CHD death, nonfatal and fatal strokes, coronary and noncoronary revascularizations, and major vascular events (total CHD, total stroke, or revascularizations) with simvastatin therapy.¹² *In the trials of statin therapy with hyperlipidemia, the relative benefit appears to be similar between diabetic patients and nondiabetic patients* (option D).

Secondary prevention: For patients with diabetes and known cardiovascular disease, high-intensity statin therapy is recommended according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines of 2013 (option A).¹³ Primary prevention: For patients with diabetes under age 40 with one additional cardiovascular risk factor or those age 40 to 75 without any cardiovascular risk factors, moderate to high-intensity statins are recommended (option B). In a pooled analysis from the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering) trials, patients with prediabetes treated with high-intensity compared to low-intensity statins were more likely to develop new onset diabetes over 5 years (HR 1.20, 95% CI; 1.04–1.37) (option E).¹⁴

28-9. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 28*) For men over age 50 and women over age 60 with at least one additional major cardiovascular risk factor, aspirin therapy at 81 mg daily is recommended as a primary prevention statin strategy for type 1 and type 2 diabetic patients (option A). *Clopidogrel is not recommended for primary prevention among diabetic patients among patients who can take aspirin* (option B). However, for men under age 50 and women under age 60 with no additional major risk factors, aspirin therapy is not recommended (option C).¹ The use of antiplatelet therapy is the mainstay of management of acute coronary syndromes in diabetic patients. With the advent of newer antiplatelet drugs, there have been recommendations for greater use of prasugrel and ticagrelor. The evidence suggests that there is no heterogeneity in the response to newer agents and strategies based on diabetes status (option D).¹⁵⁻²⁰ The optimal strategy and regimen in diabetic patients is still elusive and remains the question of ongoing trials focused on limiting the thrombotic burden and not increasing the risk of major bleeding. Clopidogrel is associated with a lower bleeding risk than are prasugrel and ticagrelor (option E).

28-10. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 28*) The significant increase in major microvascular and macrovascular complications makes it important to begin screening for diabetes at an age younger than 45 years.²¹ It has become necessary to implement aggressive screening strategies to be able to identify populations at the highest risk of developing diabetes.²² Current measures of cardiovascular surveillance for coronary artery disease (CAD) in asymptomatic diabetic patients focus on routine stress testing in accordance with the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Exercise testing in diabetic patients is more likely to be accurate when combined with echocardiography or radionuclide imaging (option A).²³ Diabetic patients are less likely to have an appropriate blood pressure and heart rate response to exercise and less likely to experience any pain corresponding to ST-segment changes caused in part by autonomic dysfunction (option B). The AHA recommends that the finding of subclinical CAD should prompt clinicians to initiate more aggressive preventive measures (option C). The DIAD study has shown that the prevalence of silent ischemia in the diabetic population is not insignificant, but the annual cardiac event rate is < 1% overall at 4.8 years of follow-up, and routine screening for inducible coronary ischemia did not reduce cardiovascular events (option D).²⁴

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CHAPTER 29

Hyperlipidemia

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

29-1. Lipoproteins contain which of the following?

- A. Neutral lipid
- B. Nonesterified cholesterol
- C. Phospholipid
- D. Proteins
- E. All of the above

29-2. A 40-year-old man with a history of hyperlipidemia has an inferior MI. Multiple members of his family have had coronary events in their early 40s. Which of the following types of studies do *not* provide evidence to support the idea that an elevated plasma LDL is a major risk factor for atherosclerotic cardiovascular disease (ASCVD)?

- A. Animal studies
- B. Genetic forms of elevated LDL
- C. Epidemiological associations
- D. Randomized controlled trials
- E. All of the above support the idea

29-3. Which of the following steps in the progression of atherosclerosis is *incorrect*?

- A. Accumulation of large numbers of foam cells gives rise to fatty streaks
- B. Some foam cells die and release their cholesterol esters into the interstitium, and over time the core of extracellular lipid expands
- C. Osteoclasts from the medium begin to produce fibrous connective tissue
- D. This tissue forms a covering of the fatty streak; here the lesion is called a fibrous plaque (fibroatheroma)
- E. Continuous filtration of LDL into the arterial wall leads to several steps to plaque progression

29-4. Which of the following is *not true* about familial hypercholesterolemia (FH)?

- A. Heterozygous FH occurs in about one in 500 persons; homozygous FH occurs in only one in a million persons
- B. Patients with heterozygous FH commonly develop premature ASCVD, most often between the ages of 30 and 60 years, and estimates are that it accounts for at least 2% of premature myocardial infarctions (MIs). Homozygous FH leads to very premature disease, often in the teens or earlier
- C. A clinical feature of FH is the presence of cholesterol deposition in tendons (xanthomas) of the hands, elbows, knees, and feet, especially the Achilles tendon
- D. Deposition of cholesterol in the skin about the eyes is called xanthelasma
- E. In individuals with hypercholesterolemia, the presence of xanthelasmas is pathognomonic of FH

29-5. One of your patients is morbidly obese and consults you with respect to the advisability of bariatric surgery. Which of the following is *not true* about obesity?

- A. Excess body weight can be defined as *overweight* (body mass index [BMI] 25 to 30 kg/m²) and *obesity* (BMI > 30 kg/m²)
- B. More than one-third (34.9% or 78.6 million) of US adults are obese
- C. More than 15% of American children and teens are clinically obese
- D. Non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%)
- E. Obesity is higher among middle-aged adults (ages 40 to 59 years; 39.5%) than among younger adults (ages 20 to 39)

years; 30.3%) or older adults (\geq age 60 years; 35.4%)

- 29-6.** A patient is referred to you with the possible diagnosis of metabolic syndrome. Which of the following is *not true* about the criteria used for the clinical definition of the metabolic syndrome?
- A. Increased blood pressure is one of the criteria
 - B. Dyslipidemia (increased triglycerides and lowered HDL-C) is one of the criteria
 - C. Increased fasting glucose is one of the criteria
 - D. Abdominal obesity (increased waist circumference) is one of the criteria
 - E. Any three of five abnormal findings constitute a diagnosis of the metabolic syndrome, and a single set of cut points are used for all components
- 29-7.** One of your patients has suffered from multiple MIs yet is statin-intolerant. You are considering starting the patient on a PCSK9 inhibitor. Which of the following is *not true* about PCSK9 inhibitors?
- A. PCSK9 inhibitors bind PCSK9 from the circulation and thereby prevent the action of PCSK9 to promote the degradation of LDL receptors
 - B. As a result of PCSK9 inhibition, fewer LDLRs are expressed by the liver, and serum LDL-C levels are reduced
 - C. US Food and Drug Administration (FDA)–approved PCSK9 inhibitors are evolocumab and alirocumab
 - D. These drugs must be given systemically once or twice a month, and they cause marked incremental reductions of LDL-C even when given with statins
 - E. To date, they appear to be safe and have not been reported to cause myopathy
- 29-8.** Which of the following is *true* about cholesteryl ester transfer protein (CETP) inhibitors?
- A. CETP inhibitors inhibit CETP, which transfers cholesterol ester from HDL-C to VLDL or LDL. As a result, HDL-C levels are increased, whereas VLDL-C and LDL-C are decreased
 - B. Three randomized controlled trials with CETP inhibitors have failed to show an ASCVD risk reduction
 - C. Torcetrapib gave an increase in total mortality, and the trial was discontinued
 - D. Trials with two other CETP inhibitors, dalcetrapib and evacetrapib, were discontinued before completion because of futility
 - E. All are true
- 29-9.** A 73-year-old woman who was recently started on a statin comes to you complaining of muscle pain. According to the 2014 National Lipid Association Statin Muscle Safety Task Force, which of the following terms is *incorrect* with respect to statin-associated adverse muscle events?
- A. Myalgia: A symptom of muscle discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level. Myalgia symptoms can be described as flu-like symptoms
 - B. Myopathy: Muscle weakness (not due to pain), with or without an elevation in CK level
 - C. Myositis: Muscle inflammation
 - D. Myonecrosis: Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex: Mild: 3- to 5-fold elevation in CK above baseline; moderate: 5- to 10-fold elevation in CK above baseline; severe: 10-fold or greater elevation in CK above baseline or an absolute level of 10,000 U/L or more
 - E. Clinical rhabdomyolysis: Myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of least 0.5 mg/dL [44 μ M/L])
- 29-10.** A patient in your practice cannot tolerate high-dose statin therapy. Which of the following statements is *not true* regarding alternatives for patients who are statin intolerant?
- A. Efforts should be doubled to start and maintain lifestyle modification, which can lower cholesterol levels by 10% to 15%
 - B. Both bile acid resins and ezetimibe can lower LDL-C by 25% to 35%
 - C. Ezetimibe plus a moderate-intensity statin will reduce cholesterol levels as much as high-intensity statins
 - D. Fibrates and niacin are alternative add-on drugs for patients with hypertriglyceridemia
 - E. In patients with severe hypercholesterolemia, PCSK9 inhibitors may be an option for patients who are statin intolerant, especially in those with ASCVD or very high LDL-C levels

ANSWERS

- 29-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 29*) The basic structure of all lipoproteins is similar. They contain a core of neutral lipid (triglyceride and cholesterol ester) (option A) that is surrounded by a polar coat containing nonesterified cholesterol (option B), phospholipid (option C), and proteins (called apolipoproteins) (option D). The major categories of lipoproteins consist of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), high-

density lipoprotein (HDL), and chylomicrons. These lipoproteins vary in size and density. Because lipoproteins can be separated by electrophoresis, they also have been named according to their migration relative to serum proteins. LDL is called beta lipoprotein, VLDL is pre-beta lipoprotein, and HDL is alpha lipoprotein.

- 29-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 29*) An elevated plasma LDL is designated a major risk factor for ASCVD. Several lines of evidence support a strong association: animal studies (option A), genetic forms of elevated LDL (option B), epidemiological associations (option C), and randomized controlled trials (RCTs) of LDL-lowering therapies (option D).
- 29-3. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 29*). Steps in the progression of atherosclerosis have been studied in detail. Accumulation of large numbers of foam cells gives rise to fatty streaks (option A). Some foam cells die and release their cholesterol esters into the interstitium, and over time the core of extracellular lipid expands (option B). Later, smooth muscle cells (*not osteoclasts*) from the medium begin to produce fibrous connective tissue (option C). This tissue forms a covering for the fatty streak; here the lesion is called a fibrous plaque (fibroatheroma) (option D). Continuous filtration of LDL into the arterial wall leads to several steps to plaque progression (option E); after many years, atheromas degenerate into complicated lesions, become unstable, and are prone to rupture. When rupture occurs, plaque material discharges into the lumen of the artery, producing thrombosis and cardiovascular events. At any stage of this process, LDL-lowering therapy reduces plaque progression and decreases the likelihood of plaque rupture and acute ASCVD events.
- 29-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 29*). Classic estimates were that heterozygous FH occurs in about one in 500 persons; homozygous FH occurs only one in a million persons (option A). In some populations, the prevalence of both forms can be higher. Patients with heterozygous FH commonly develop premature ASCVD, most often between the ages of 30 and 60 years, and estimates are that it accounts for at least 2% of premature MIs. Homozygous FH leads to very premature disease, often in the teens or earlier (option B). Another clinical feature of FH is the presence of cholesterol deposition in tendons (xanthomas) of the hands, elbows, knees, and feet, especially the Achilles tendon (option C). Deposition of cholesterol in the skin about the eyes is called xanthelasma (option D); in individuals with hypercholesterolemia, this finding suggests but is not pathognomonic of FH (option E). The same is true for corneal arcus.
- 29-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 29*). Obesity in the general population is associated with an increased risk of ASCVD and other disorders. Among the latter are hypertensive cardiovascular disease, type 2 diabetes, fatty liver disease, gallstone disease, obstructive sleep apnea, and certain forms of cancer (colon, breast, and endometrial). Excess body weight can be defined as *overweight* (BMI 25 to 29 kg/m²) (*not BMI 25-30 kg/m²*) and *obesity* (BMI ≥ 30 kg/m²) (*not BMI > 30 kg/m²*) (option A). According to the Centers for Disease Control and Prevention (CDC), more than one-third (34.9% or 78.6 million) of US adults are obese (option B). In addition, more than one-third of American adults (35.7%) and 17% (12.5 million) of American children and teens are clinically obese (option C). The CDC notes that non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%), followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%) (option D). Moreover, obesity is higher among middle-aged adults (ages 40 to 59 years; 39.5%) than among younger adults (ages 20 to 39 years; 30.3%) or older adults (≥ age 60 years; 35.4%) (option E).
- 29-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 29*). A clinical diagnosis of the metabolic syndrome can be made in accord with a clinical definition.¹ The risk factors of this definition include increased blood pressure (option A), dyslipidemia (increased triglycerides and lowered HDL-C) (option B), increased fasting glucose (option C), and abdominal obesity (increased waist circumference) (option D). This diagnosis harmonized previous recommendations from the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute. Any three of five abnormal findings constitute a diagnosis of the metabolic syndrome. A single set of cut points is used for all components *except waist circumference, for which different national or regional thresholds for waist increased circumference were recommended* (option E).
- 29-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 29*). Monoclonal antibody inhibitors of PCSK9 are a new class of LDL-lowering drugs. They bind PCSK9 from the circulation and thereby prevent the action of PCSK9 to promote the degradation of LDL receptors (option A).^{2,3} As a result, more (*not fewer*) LDLRs are expressed by the liver, and serum LDL-C levels are reduced (option B).^{4,5} US Food and Drug Administration (FDA)–approved PCSK9 inhibitors are evolocumab^{4,5} and alirocumab (option C).⁶ Another agent (bococizumab) is under investigation. These drugs must be given systemically once or twice a month. They cause marked incremental reductions of LDL-C even when given with statins (option D). To date, they appear to be safe and have not been reported to cause myopathy (option E). Interim reports from randomized controlled trials (RCTs) indicate that they enhance risk reduction in high-risk patients treated with statins.^{7,8} Meta-analysis of several smaller trials further suggests ASCVD benefit.⁹
- 29-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 29*). CETP inhibitors inhibit CETP.¹⁰ The protein transfers cholesterol ester from HDL-C to very-low-density or low-density lipoproteins (VLDL or LDL). As a result, HDL-C levels are increased, whereas VLDL-C and LDL-C are decreased (option A). This exchange theoretically could be beneficial by raising HDL-C, the so-called good cholesterol. However, to date three randomized controlled trials (RCTs) with CETP inhibitors have failed to show an ASCVD risk reduction (option B). One inhibitor, torcetrapib, gave an

increase in total mortality, and the trial was discontinued (option C).¹¹ Trials with two other CETP inhibitors, dalcetrapib and evacetrapib, were discontinued before completion because of futility (option D).¹²

- 29-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 29*). Although the main concern with statins is the risk of rhabdomyolysis, this is a rare occurrence that affects 0.1% of patients.^{13,14} Terminology relating to statin-associated adverse muscle events is variable and has changed over time. According to the 2014 National Lipid Association Statin Muscle Safety Task Force:¹³ Myalgia: A symptom of muscle discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level. Myalgia symptoms can be described as flu-like symptoms (option A). Myopathy: Muscle weakness (not due to pain), with or without an elevation in CK level (option B). Myositis: Muscle inflammation (option C). Myonecrosis: Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex: *Mild: 3- to 10-fold elevation in CK above baseline; Moderate: 10- to 50-fold elevation in CK above baseline; Severe: 50-fold or greater elevation in CK above baseline or an absolute level of 10,000 U/L or more* (option D). Clinical rhabdomyolysis: Myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of least 0.5 mg/dL [44 μM/L]) (option E).
- 29-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 29*). Statins are first-line cholesterol-lowering therapy, but if they are not tolerated, other ways to achieve cholesterol goals can be considered. Efforts should be doubled to start and maintain lifestyle modification, which can lower cholesterol levels by 10% to 15% (option A).¹⁵ Both bile acid resins and ezetimibe can lower LDL-C by 15% to 25% (*not 25% to 35%*) (option B). Ezetimibe plus a moderate-intensity statin will reduce cholesterol levels as much as high-intensity statins (option C). Fibrates and niacin are alternative add-on drugs for patients with hypertriglyceridemia (option D). Finally, in patients with severe hypercholesterolemia, PCSK9 inhibitors may be an option for patients who are statin intolerant, especially in those with ASCVD or very high LDL-C levels (option E).

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SECTION 6

Cigarette Smoking and Cardiovascular Disease

CHAPTER 30

Epidemiology of Smoking and Pathophysiology of Cardiovascular Damage

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

30-1. At its peak in the 1960s, what proportion of the United States population consumed cigarettes?

- A. 35%
- B. 45%
- C. 55%
- D. 65%
- E. 75%

30-2. What proportion of the world's 1 billion smokers are male?

- A. 50%
- B. 60%
- C. 70%
- D. 80%
- E. 90%

30-3. Which of the following statements concerning smoking prevalence and trends in the United States is *false*?

- A. The prevalence of smoking among adults in the US decreased by 25% between 1998 and 2013
- B. Smoking among US high school students decreased by > 50% between 1997 and 2013
- C. A larger proportion of adults 20 to 49 years of age smoke compared to adults age 50 and older
- D. Hispanic men are almost twice as likely to smoke as Hispanic women
- E. All of the above are true

30-4. By approximately how many years does smoking throughout adulthood reduce life expectancy?

- A. 2 years
- B. 5 years
- C. 7 years
- D. 10 years
- E. 12 years

30-5. Which of the following statements concerning smoking and cardiovascular disease is *false*?

- A. Smoking increases the risk of peripheral arterial disease and abdominal aortic aneurysm by fivefold
- B. Smoking increases the risk of ischemic heart disease and stroke by threefold
- C. There is a linear and independent relationship between smoking duration and intensity and increasing arterial stiffness
- D. Only three constituents of cigarette smoking have been shown to play a role in the initiation and progression of cardiovascular disease: nicotine, carbon monoxide, and reactive oxygen species
- E. Cigarette smoking disrupts cardiovascular homeostasis, leading to hemodynamic changes, endothelial dysfunction, inflammation, thrombosis and plaque progression, and abnormalities in lipid and glucose metabolism

30-6. Which of the following statements concerning the effects of cigarette smoking is *false*?

- A. Nicotine consumption results in acute, but not chronic, increases in heart rate up to 7 to 10 beats per minute, and elevation in systolic blood pressure up to 5 to 10 mm Hg

- B. A combination of nicotine-induced increased oxygen demands and carbon monoxide-associated reduced oxygen availability may lower the threshold for angina onset in smokers
- C. The primary mechanism by which smoking leads to vascular and endothelial dysfunction is thought to be suppression of endothelial nitric oxide synthase (eNOS) expression and subsequent decreased bioavailability of NO caused by oxidant chemicals from cigarette smoke
- D. Cigarette smoking promotes a prothrombotic state through alterations in platelet activity as well as antithrombotic and prothrombotic factors, including fibrinolytic factors and platelet-mediated pathways
- E. Chronic vascular inflammation mediated by cigarette smoking may play an important role in the progression of atherosclerosis

30-7. Smokers are how much more likely to have diabetes than individuals who have never smoked?

- A. 0% (incidence of diabetes is not affected by smoking)
- B. 25%
- C. 45%
- D. 65%
- E. 100%

30-8. Which of the following statements concerning electronic cigarettes (e-cigarettes) is *false*?

- A. There are currently no results from appropriately powered randomized controlled trials examining e-cigarettes for smoking cessation
- B. Studies looking at the long-term safety of e-cigarettes are lacking
- C. Population-based studies suggest e-cigarette use is associated with 28% lower odds of quitting compared to nonusers
- D. The use of e-cigarettes by youth is increasing
- E. E-cigarettes are marketed for therapeutic purposes in the United States

30-9. Which of the following statements concerning smoking cessation in cardiovascular patients is *false*?

- A. Smokers with myocardial infarction are more likely to quit than similar patients undergoing percutaneous coronary intervention (PCI) who did not present with myocardial infarction
- B. Patients with cardiovascular disease who continue to smoke have nearly double the risk of death, myocardial infarction, or stroke compared to patients who quit
- C. Patients who quit smoking after PCI have fewer anginal episodes within the first year than patients who continue to smoke
- D. Only one in three smokers hospitalized with acute coronary syndrome (ACS) remains abstinent following discharge
- E. Varenicline does not increase abstinence following ACS

30-10. What public health intervention has had the largest impact on cigarette consumption?

- A. Taxation of tobacco
- B. Restrictions on tobacco advertisements
- C. Policies to reduce exposure to secondhand smoke
- D. Graphic warnings on cigarette packs
- E. Public quitlines

ANSWERS

30-1. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 30*) Although the Surgeon General's report in 1957 concluded that cigarette smoking is associated with an increased risk of lung cancer, it was not until publication of the landmark 1964 Surgeon General's report that the adverse relationship between cigarette smoking and cardiovascular disease was seriously recognized. The Surgeon General's report concluded that cigarette smoking is strongly associated with myocardial infarction and coronary heart disease deaths, and it laid the foundation for tobacco control.¹ Unfortunately, health care providers, professional societies, civic bodies, and governments have also played negative or timid roles, largely attributed to the smoking industry's exploitation of the natural skepticism and probabilistic nature inherent in scientific evidence, serious conflicts of interest, and lack of a strong public will. Smoking has claimed more than 20 million lives with premature deaths in the United States alone since the publication of the 1964 report. The annual per capita cigarette consumption in the United States was at its peak in the early 1960s, with a prevalence smoking of about 45% of the population in 1965 (option B). Through concerted efforts over more than half a century, the cigarette consumption in the United States has declined to half of its peak prevalence rates—to about 18% in 2012.² Multiple factors, including an improved understanding of the adverse effects of secondhand smoke, policy measures such as a ban on broadcast advertising, increased public awareness, and the increase in cigarette taxes have contributed to this epidemiological transition. Despite years of progress, cigarette smoking remains the leading cause of preventable

cardiovascular morbidity and mortality across the globe.

- 30-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 30*) Globally, about 1 billion individuals smoke. The majority (about 800 million) are males (80%, option D). Although the prevalence of smoking has declined over the past few decades, the total number of smokers has increased globally owing to population growth. The worldwide prevalence of smoking is highly variable by country and region, suggesting a heavy influence of socioeconomic and cultural currents as well as national policies. In 2012, the prevalence of smoking among adults was 49% in eastern Europe, 45% in China, 36% in Japan, 28% in western Europe, 23% in India, and about 18% in Australia, the United States, and Canada.³ When considering differences by age groups, the highest prevalence of smoking worldwide in 2012 was seen in males aged 44 to 49 (41% prevalence) and females aged 50 to 54 (8.7% prevalence). There is a disproportionately high burden of smoking among males compared to females in countries such as China and India. This is also reflected in the recent estimates of deaths attributable to smoking in China; of the nearly 1 million deaths in 2010, 840,000 were among males in contrast to 130,000 among females.⁴ A high burden of smoking among adolescents and young adults (more than 150 million smokers were 25 years or younger) remains a major concern and challenge.³ During 2012, the prevalence of smoking among 20- to 24-year-old males was above 50% in eastern Europe, Russia, and Indonesia, 41% in China, 37% in Japan, 28% in Latin America, 24% in Pakistan, 21% in Australia, 19% in Canada and the United States, and 13% in India.
- 30-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 30*) According to the Behavioral Risk Factor Surveillance System (BRFSS) survey, the prevalence of smoking among US adults has declined by 25%, with only 17.9% smokers in 2013 as compared to 24.1% smokers in 1998 (option A).⁵ A larger change in smoking prevalence has been seen among US high school students: 15.7% in 2013 compared to 36.4% in 1997 (option B). There are important differences in the smoking prevalence by states and regions in the United States. Similarly, US population-based survey data (National Health and Nutrition Examination Survey [NHANES]) for 2011–2012 showed a much higher smoking prevalence among people 20 to 49 years of age (23.1%) compared to those 50 years of age and older (16.3%) (option C).⁵ There is significant heterogeneity in smoking prevalence by race/ethnicity and gender. The smoking rate among Hispanic men (16%) is almost two times higher than it is among Hispanic women (8.3%) (option D).
- 30-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 30*) A loss of about a decade of life expectancy is estimated because of smoking throughout adulthood among both men and women in various countries, including the United Kingdom, the United States, Japan, and India (option D).⁶ Importantly, people who have smoked cigarettes since early adulthood but stopped at 30, 40, or 50 years of age gain back 10, 9, and 6 years of life expectancy, respectively.⁶ About 5 to 6 million yearly deaths worldwide and about 0.5 million in the United States are attributable to cigarette smoking each year. This estimate is projected to increase to more than 10 million in a few decades.^{6,7} In 1990, smoking was the third-ranked risk factor after childhood malnutrition and indoor pollution from biofuels for loss of disability-adjusted life years (ie, sum of years of life lost and years lived with disability [DALY]). With improvements in nutrition and clean fuel availability, in 2010, it has become the second most common contributor to loss of DALYs (6.3%; 95% confidence interval, 6.2 to 7.7).⁸ Smoking is the highest contributor to loss of DALYs in males worldwide and in both males and females in many developing countries. The US societal costs of cigarette smoking per year are around \$289 billion; this includes about \$151 billion in lost productivity caused by premature deaths and remaining as direct health care costs.⁵
- 30-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 30*) Smoking has been associated with increased and accelerated atherosclerosis and acute plaque rupture and all cardiovascular end points, including myocardial infarction, stroke, and peripheral arterial disease.⁹ While smoking causes incremental and independent risk with other risk factors such as hypertension and diabetes on coronary and cerebral vasculature, its prominent role in peripheral vasculature and small-vessel disease has been appreciated: fivefold increased risk of peripheral arterial disease and abdominal aortic aneurysm (option A) compared to a 1.5- to 2-fold increased risk of ischemic heart disease and stroke (option B).¹⁰ A linear and independent relationship of smoking duration and intensity has been reported, with an increase in arterial stiffness measured using brachial-ankle pulse wave velocity (option C).¹¹ Cigarette smoke is a mixture of more than 5000 toxic chemicals¹² and 1015 to 1017 free radicals.^{13,14} It is conventionally divided into two chemically different phases: a tar phase and a gas phase.¹⁵ The tar or particulate phase is material that is trapped when the smoke steam is passed through the glass-fiber (cigarette) filter. The cigarette filter retains 99.9% of all particles larger than 0.1 μm . Nicotine is a major chemical component of the particulate phase of cigarette smoke.¹⁶ The gas (or vapor) phase consists of the material that passes through the cigarette filter.¹⁶ The common chemical components of the gas phase include carbon monoxide (CO), acetaldehyde, formaldehyde, acrolein, nitrogen oxides, and carbon dioxide. Both phases are high in reactive oxygen species (ROS).¹⁷ Despite the presence of many constituents in both phases, only three constituents (nicotine, CO, and ROS) have been shown to play a role in the initiation and progression of cardiovascular disease (option D).¹⁸ The net effect of various endogenous chemicals from cigarette smoke, such as oxidative free radicals and nicotine, together with inflammatory molecules and endogenous-produced ROS released by activated inflammatory cells, is disruption of cardiovascular homeostasis, leading to hemodynamic changes, endothelial dysfunction, inflammation, thrombosis and plaque progression, and abnormalities in lipid and glucose metabolism (option E).¹⁴
- 30-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 30*) Via sympathetic stimulation, nicotine leads to an increase in cardiac contractility, acute and chronic increase in heart rate up to 7 to 10 beats per minute,¹⁹ and elevation in systolic

blood pressure up to 5 to 10 mm Hg from baseline (option A).¹⁸ Carbon monoxide (CO) is another component of cigarette smoke that has been implicated in cigarette smoke-induced hemodynamic changes. By binding to hemoglobin, CO reduces the oxygen-carrying capacity of hemoglobin, resulting in relative hypoxemia and subsequent dilation of coronary arteries.²⁰ A combination of nicotine-induced increased oxygen demands on one side and CO-associated reduced oxygen availability on the other side may lower the threshold for angina onset in smokers (option B).²¹ Cigarette smoking-induced endothelial dysfunction is an important factor in coronary hemodynamic disturbances and the progression of atherosclerosis. The primary mechanism by which smoking leads to vascular and endothelial dysfunction is thought to be suppression of eNOS expression and subsequent decreased bioavailability of NO caused by oxidant chemicals from cigarette smoke (option C).²² Cigarette smoking has also been shown to promote a prothrombotic state through several mechanisms. These mechanisms include alterations in platelet activity as well as alterations in antithrombotic and prothrombotic factors, including fibrinolytic factors and platelet-mediated pathways (option D).^{15,23} Chronic vascular inflammation mediated by cigarette smoking may play an important role in the progression of atherosclerosis (option E).²⁴ The exact molecular-pathogenic mechanisms by which smoking induces vascular inflammation are not completely established. Nonetheless, the role of several proinflammatory cytokines as well as activation and interaction between leukocytes and endothelial cells is well recognized in this process.

- 30-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 30*) Cigarette smoking increases the risk of development of diabetes mellitus type 2.²⁵ A dose-response relationship has been found between the smoking and the incidence of diabetes mellitus in both men and women.²⁶ Data from the Cancer Prevention Study have shown that there is a 45% higher diabetes rate among smokers than among men who had never smoked (option C). Higher levels of HbA1C have been found in smokers with diabetes than in nonsmokers with diabetes. Smoking also increases requirements for insulin and causes insulin resistance in nondiabetics.²⁷ Studies have also shown an increased risk of microvascular complications of diabetes such as diabetic neuropathy and faster progression of renal disease.²⁸ There has been a debate about whether possible weight gain associated with quitting smoking is associated with increased risk, too.²⁹ Although confounding in observational studies makes it difficult to test this relationship further, the increased risk of weight gain after cessation ameliorates with the duration of smoking cessation.²⁹ The pathogenesis of smoking and glucose metabolism is not well understood, but nicotine appears to have a central role in this process.^{14,30} Nicotine stimulates catecholamine release from the adrenal medulla and sympathetic nervous system, which may lead to insulin resistance. It also increases the release of corticosteroids, which are known hyperglycemic hormones.¹⁸
- 30-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 30*) Invented in the early 2000s by a Chinese pharmaceutical company and patented in 2004, e-cigarettes deliver a nicotine-containing vapor when a solution of nicotine with humectant solution (glycerol or propylene glycol) and flavoring is heated by a battery-powered atomizer. Currently, there are no appropriately powered randomized controlled trials with e-cigarettes to examine their efficacy in smoking cessation (option A).³¹ Also, studies looking at the long-term safety of e-cigarettes are lacking (option B). When using population-based studies of smoking cessation in the absence of good randomized controlled trials, e-cigarette users are associated with 28% lower relative odds of quitting compared to nonusers (option C).³² There are growing concerns about their use due to the absence of studies showing either safety or efficacy. For instance, among high school students, the use of e-cigarettes tripled in 2014 to 2 million (13.4%) from 0.67 million (4.5%) in 2013 (option D).³³ Because of a lack of evidence supporting the safety or efficacy of e-cigarettes at this time, e-cigarette companies cannot advertise them as an alternative for smoking cessation or for therapeutic purposes in the United States (option E).
- 30-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 30*) In a retrospective analysis of over 2000 patients who underwent percutaneous coronary intervention (PCI) from 1999 to 2009 at Olmsted County, Minnesota, smoking cessation rates at 6 to 12 months were around 50% and did not change over a decade.³⁴ The odds of cessation were 2.6 times higher among those who had presented with myocardial infarction (option A) and three times among those who participated in cardiac rehabilitation, and cessation was associated with better prognosis.³⁴ Similarly, a cessation rate of about 60% was seen in Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial participants, and those who continued to smoke had a 1.8 times higher risk of death, myocardial infarction, or stroke compared to those who had quit (option B).³⁵ Smokers have worse outcomes than nonsmokers after PCI, and those who quit smoking after PCI had fewer anginal episodes at 1-year follow-up than those who continued (option C).³⁶ It is a big challenge and a big opportunity for us that less than one in three of the current smokers hospitalized with acute coronary syndrome (ACS) remains abstinent following discharge (option D). In a recent study of patients presenting with ACS, varenicline was associated with an abstinence rate of 47.3% versus 32.5% in the placebo group at 6 months (option E).³⁷
- 30-10. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 30*) The most common and successful step that has been used to reduce tobacco consumption is excise taxes (option A). About a 20% decrease in cigarette consumption has been reported with a 50% increase in inflation-adjusted tobacco price.³⁸ Tobacco taxes have proven to be more effective among younger adults, and among poor or less educated groups.⁶ However, a rapid growth in income and purchasing power parity in developing countries, and the availability of low-priced alternatives such as "bidis," is a challenge. The lower excise tax in the low-income countries makes cigarettes cheaper than in developed countries. Additionally, organized smuggling of cigarettes after excise taxes are raised remains another challenge that will require stricter tax administration.⁶ Profits from tobacco manufacturing exceeded 50 billion US dollars in 2012,³⁹ and beyond the industry's

lobbying effort for keeping a check on excise taxes, the major portal for more than half a century has been the influence and use of mass media. Although a complete or partial ban on tobacco advertisements remains a strong tool to reduce smoking rates, comprehensive bans may be needed to prevent the tobacco industry from using advertising media (option B).⁶ Legislative developments to protect people from secondhand smoke (option C), research to continue to study the influence of various interventions to reduce smoking rates, and understanding the counterforces, such as smoking industry activities and human behavior, will be important. Other interventions, such as graphic warnings on cigarette packs (option D) and public quitlines (option E), have been used to reduce tobacco consumption.

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CHAPTER 31

Preventing and Mitigating Smoking-Related Heart Disease

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 31-1.** What percentage of smokers interested in quitting are reported to have received tobacco cessation medication during outpatient physician office visits?
- A. 69%
 - B. 50%
 - C. 21%
 - D. 8%
 - E. 75%
- 31-2.** Which of the following statements about the cardiovascular benefits of smoking cessation is *false*?
- A. In one year following smoking cessation, half the excess risk of a myocardial infarction is gone
 - B. Smoking cessation before the age of 30 years eliminates nearly all the risk of death from smoking-related disease
 - C. The risk of cardiac events drops approximately one month after quitting smoking
 - D. Those who quit when they are older gain years of life compared to those who continue to smoke
 - E. The risk of myocardial infarction and other cardiac events drops 15% to 20% by a month after implementing comprehensive smoke-free laws to protect people from secondhand smoke
- 31-3.** Which of the following statements is *not* included within the US Public Health Service “5As” model for smoking cessation intervention and screening for tobacco use?
- A. *Advocate* for patients who wish to quit smoking
 - B. *Advise* tobacco users to quit
 - C. *Arrange* for follow-up to monitor progress
 - D. *Assist* patients interested in quitting with counseling and/or pharmacotherapy
 - E. *Assess* patient interest in and willingness to quit
- 31-4.** A 52-year-old female smoker presents to your clinic and expresses her desire to quit smoking. Which of the following treatment options should *not* be recommended to your patient as a first-line therapy for smoking cessation?
- A. Nicotine patch
 - B. Electronic cigarette
 - C. Varenicline
 - D. Bupropion
 - E. Nicotine inhaler
- 31-5.** A 43-year-old male smoker expresses his desire to quit smoking. He says he has previously tried to quit cold turkey but was unable to abstain from smoking in the long run. What is the maximum recommended duration of nicotine replacement therapy (NRT) use?
- A. 8 weeks
 - B. 10 weeks
 - C. 12 weeks
 - D. 24 weeks
 - E. 52 weeks
- 31-6.** Which of the following interventions has *not* been associated with long-term smoking cessation compared with sham interventions?

- A. Motivational interviewing
- B. Printed self-help materials
- C. Acupuncture
- D. Telephone counseling
- E. Mobile phone-based interventions

31-7. A smoker with two previous quit attempts is interested in combining NRT with a second form of pharmacotherapy. Which of the following statements about combination therapy is *correct*?

- A. Treatment with a combination of long-acting and short-acting NRT is not associated with increased smoking cessation when compared to a single type of NRT
- B. Varenicline combined with NRT is associated with higher tobacco abstinence at 12 weeks and 6 months compared to varenicline alone
- C. Participants receiving combination therapy do not report more anxiety and depressive symptoms
- D. Combination of bupropion and NRT treatment is associated with a significant difference in smoking cessation compared to NRT alone
- E. There is no evidence that combination therapy is effective for smoking cessation

31-8. A 30-year-old man who self-identifies as a social smoker (5 or fewer cigarettes per day) presents to your clinic for an unrelated clinical concern. He is unbothered by his smoking, which he does *not* feel compelled to reduce due to his already low number of cigarettes smoked per day. Which of the following statements about the health effects of smoking reduction is *true*?

- A. The dose-response relationship between smoking and cardiovascular disease is highly linear
- B. Smoking reduction has not been associated with improved levels of biomarkers associated with cardiovascular disease in some studies
- C. Smoking as few as five cigarettes a day is associated with a higher risk of death from ischemic heart disease
- D. Cigarette smoking at low levels is not associated with an increased risk of cardiovascular disease
- E. Complete cessation should not be encouraged in all patients

31-9. The World Health Organization's Framework Convention on Tobacco Control (FCTC) emphasizes the importance of promoting public health through the implementation of policies, including which of the following?

- A. Smoke-free environments to protect people from secondhand smoke and to provide an environment that helps people stop smoking
- B. Elimination of tobacco advertising and promotion
- C. Increased taxes to reduce demand for cigarettes
- D. Education of the public on the risks of smoking, such as with large graphic warning labels on tobacco products
- E. All of the above

31-10. A 21-year-old smoker is interested in finding alternatives to cigarette smoking and asks about using electronic cigarettes (e-cigarettes) to help him quit smoking. Which of the following statements about e-cigarettes is *false*?

- A. E-cigarettes are relatively new products, so their long-term health effects are unknown
- B. As of January 2016, e-cigarettes were regulated by the FDA
- C. As currently being used in the real world, e-cigarettes are associated with significantly less quitting than NRT or no cessation aids
- D. E-cigarettes should not be recommended as effective smoking cessation aids until there is evidence that they assist in smoking cessation
- E. Use of e-cigarettes by patients may signal readiness to quit cigarettes, and thus clinicians should be prepared to support patients in their quit attempts

ANSWERS

31-1. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 31*) Even though 69% of smokers are interested in quitting (option A) and over half report having made a quit attempt in the past year (option B),¹ only 21% of adult current tobacco users received tobacco cessation counseling (option C) and 8% received tobacco cessation medication during outpatient visits (option D).² Screening for interest in tobacco cessation is particularly important because physician advice to quit smoking is associated with increased smoking cessation compared to no advice to quit or usual care, with higher cessation seen with more intensive advice compared to minimal advice.³ It is important that screening be incorporated into all clinical encounters, including those with cardiologists and other specialists, not only to identify and assist patients who are ready to stop smoking, but also to encourage those who are not yet ready to move toward making

the decision to quit.

- 31-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 31*) In addition to contributing to the long-term development of atherosclerosis, smoking (and secondhand smoke exposure) has immediate effects (within minutes) on endothelial function^{4,5} and platelet activation⁶ and so can trigger a cardiac event. The risk of cardiac events begins to drop immediately after quitting and declines rapidly (option C). The heart rate drops 20 minutes after quitting, and in a year, half the excess risk of a myocardial infarction is gone (option A). The risk of myocardial infarction and other cardiac events drops 15% to 20% by a month after implementing comprehensive smoke-free laws to protect people from secondhand smoke (option E).^{7,8} Smoking cessation before the age of 30 years eliminates nearly all of the risk of death from smoking-related disease (option B), and even those who quit when they are older gain years of life compared to those who continue to smoke (option D).⁴ This fact highlights both the importance of encouraging smokers to quit early and the importance of encouraging all smokers to quit, no matter how old they are.
- 31-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 31*) The US Public Health Service recommends the 5As model for smoking cessation intervention, in which providers (1) *ask* patients about tobacco use to identify current users, (2) *advise* tobacco users to quit (option B), (3) *assess* patient interest in and willingness to quit (option E), (4) *assist* patients interested in quitting with counseling and/or pharmacotherapy (option D), and (5) *arrange* for follow-up to monitor progress (option C). Although current smokers report high rates of being asked about tobacco use (88%), fewer report being advised to quit (66%), and even fewer report being asked if they wanted to quit (43%).⁹ If smokers are not properly identified, those interested in cessation cannot be connected with resources that can help them with their quit attempt. Therefore, screening should be incorporated into all outpatient and hospital encounters.
- 31-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 31*) Various prescription and nonprescription medications approved by the US Food and Drug Administration (FDA) are available to help patients in their attempt to quit, provided patients do not have contraindications to their use.¹⁰ Nicotine replacement therapy, which provides patients with nicotine to manage cravings and nicotine withdrawal symptoms, comes in a variety of forms. Types of NRT include patches (option A), lozenges, inhalers (option E), and nasal sprays. FDA-approved medications include NRT, varenicline (option C), and bupropion (option D). They are all first-line treatments for smoking cessation, and the choice of agent should take into consideration patient preferences, medical comorbidities, and potential drug-drug interactions.
- 31-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 31*) With respect to treatment duration, a randomized clinical trial of different durations of nicotine patch treatment (8, 24, or 52 weeks) found higher rates of smoking abstinence at 24 weeks in those still using nicotine patches, but no significant difference was seen at 52 weeks.¹¹ This result suggests that, while nicotine patch treatment can continue longer than 8 to 10 weeks (options A and B), evidence does not support extending treatment past 24 weeks (option D). For the timing of treatment initiation, there is some evidence that starting nicotine patches prior to a patient's quit day is associated with increased smoking cessation compared to starting after the quit day. However, no difference was seen with nicotine gum or lozenges.¹² Thus, it is not necessary to wait until the quit date to initiate treatment with nicotine patches. It is important to note that, while clinical trials have demonstrated the efficacy of NRT when used as part of an organized cessation effort, unsupervised NRT bought over the counter is associated with significantly less quitting than the use of no smoking cessation aids (odds ratio [OR] 0.68, confidence interval [CI] 0.49–0.94).¹³ Thus, patients using NRT should be followed and encouraged to maintain their quit attempt. Such combinations of counseling and NRT can be accomplished through telephone quitlines, which also provide certain types of NRT to eligible callers.
- 31-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 31*) Counseling delivered by telephone (option D), either through telephone quitlines or other sources, is associated with smoking cessation,¹⁴ as are some mobile phone-based interventions (option E),¹⁵ printed self-help materials (option B),¹⁶ and interactive, tailored Internet-based interventions.¹⁷ Motivational interviewing, which consists of counseling to improve one's motivation for and interest in behavioral change, has also been associated with increased smoking cessation compared to brief advice or usual care.¹⁸ In people using pharmacotherapy for smoking cessation, the addition of behavioral support through in-person or telephone contact is also associated with increased smoking cessation compared to control groups.¹⁹ Assistance via telephone is available from state telephone quitlines toll-free at 1-800-QUIT-NOW (1-800-784-8669). Support through text messaging can also be found through the National Cancer Institute's Smokefree TXT program, which is available at smokefree.gov/smokefreetxt, or by texting the word QUIT to 47848 from a mobile phone. Acupuncture, acupressure, or laser therapy has not been associated with long-term smoking cessation compared with sham interventions.²⁰
- 31-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 31*) Treatment with a combination of long-acting and short-acting NRT is associated with increased smoking cessation compared to a single type of NRT (option A).¹² A randomized controlled trial found that varenicline combined with NRT was associated with higher tobacco abstinence at 12 weeks and 6 months compared to varenicline alone (option B).²¹ Another randomized controlled trial found that treatment with both varenicline and bupropion for 12 weeks was associated with significantly greater smoking cessation than treatment with varenicline alone at 12 weeks (OR 1.49, 95% CI 1.05–2.12) and 26 weeks (OR 1.52, 95% CI 1.04–2.22)—but not at 52 weeks (OR, 1.32, 95% CI 0.91–1.91).²² Participants receiving combination therapy, however, reported more anxiety and depressive symptoms (option C). Combination bupropion and NRT treatment is not associated

with a significant difference in smoking cessation compared to NRT alone (option D).²³ While combining different forms of NRT is a recommended, effective strategy for smoking cessation, combination of NRT with bupropion has not proven to be effective, and while combination varenicline and NRT has shown some promise of efficacy at 6 months, further studies on long-term efficacy and safety are needed.

- 31-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 31*) Cigarette smoking, even at low levels, is associated with an increased risk of cardiovascular disease.²⁴⁻²⁶ The dose-response relationship between smoking and cardiovascular disease is highly nonlinear, with more rapid increases in risk at low levels of exposure and flattening of the curve at higher levels of exposure.²⁴ In fact, smoking as few as five cigarettes a day is associated with a higher risk of death from ischemic heart disease.²⁶ Smoking a few cigarettes a day should not be promoted as a long-term use pattern, and complete cessation should be encouraged in all patients. Smoking reduction has been associated with improved levels of biomarkers associated with cardiovascular disease in some studies,^{27,28} but not in others.²⁹ It is not clear whether improvements in these biomarkers also result in improvements in the risk of smoking-related disease.
- 31-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 31*) There is great variability in the prevalence of cigarette smoking worldwide. The World Health Organization's Framework Convention on Tobacco Control (FCTC), the first global public health treaty, adopted in 2003 and implemented in 2005, emphasizes the importance of promoting public health through the implementation of policies, including smoke-free environments to protect people from secondhand smoke and to provide an environment that helps people stop smoking; elimination of tobacco advertising and promotion; increased taxes to reduce the demand for cigarettes; and education on the risks of smoking, such as with large graphic warning labels on tobacco products.³⁰ Although the FCTC has accelerated the implementation of smoke-free laws³¹ and strong health warning labels,³² only about half of nations report 100% smoke-free restaurants and even fewer smoke-free private workplaces.³³ As of 2016, the United States was one of the few countries that had not ratified the FCTC, and the United States lags behind the rest of the world in several areas, notably strong graphic warning labels on tobacco products, restrictions on advertising and promotion, and tobacco taxation. More comprehensive smoking laws are needed worldwide to ensure the maximum health benefits conferred to both smokers and nonsmokers by such tobacco control legislation.
- 31-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 31*) As of January 2016, e-cigarettes were not regulated by the FDA. E-cigarettes, a type of electronic nicotine delivery system, are battery-powered devices that heat a solution of humectants such as propylene glycol or glycerol, generally with nicotine and/or flavorings, to form an aerosol that is inhaled by the user. E-cigarettes are relatively new products, so their long-term health effects are unknown (option A). Although many smokers report using e-cigarettes to quit smoking, randomized controlled trials on their efficacy for smoking cessation have been limited, and their results have been equivocal.^{34,35} As currently being used in the real world, e-cigarettes are associated with significantly less quitting than NRT or no cessation aids (option C).³⁶ Data from three studies³⁷⁻³⁹ suggest that specific e-cigarette use patterns (daily use of high nicotine delivery devices, which represents the minority of users in these studies) may be associated with increased quitting; as e-cigarette product types and use patterns continue to evolve, this association should continue to be studied. Nevertheless, e-cigarettes should not be recommended as effective smoking cessation aids until there is evidence that, as promoted and used, they assist in smoking cessation (option D).^{36,40} A policy statement by the American Heart Association in 2014 encourages the inclusion of e-cigarette use in tobacco screening questions.⁴¹ Use of e-cigarettes by patients may signal readiness to quit cigarettes, and thus clinicians should be prepared to support patients in their quit attempts and to discuss evidence-based practices for smoking cessation, including counseling, NRT, or stop-smoking pharmacotherapy, with these patients (option E).⁴⁰

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SECTION 7

Atherosclerosis and Coronary Heart Disease

CHAPTER 32

Atherothrombosis: Disease Burden, Activity, and Vulnerability

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

32-1. Which of the following statements is *not true*?

- A. Causal and modifiable risk factors for atherosclerotic cardiovascular disease are well known but account for < 50% of heart attacks in both sexes
- B. Individual susceptibility to conventional risk factors varies greatly, and therefore their predictive value is limited
- C. Most first heart attacks occur among people with average or only slightly elevated risk factor levels
- D. Better detection of at-risk individuals may be achieved by visualizing the diseased arterial wall rather than just assessing risk factors
- E. All of the statements are true

32-2. Which of the following statements is *not true*?

- A. Atherosclerosis is a chronic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development
- B. Atherosclerosis predominates at sites characterized by high and nonoscillatory endothelial shear stress
- C. The speed of disease progression varies greatly, but it usually takes decades to develop the advanced atherosclerotic lesions responsible for clinical disease
- D. Plaques are very heterogeneous in size and composition, even plaques located next to each other
- E. Most plaques remain asymptomatic, some become obstructive, and a few, if any, become vulnerable

32-3. Which of the following statements is *not true*?

- A. Approximately 50% of symptomatic coronary thrombi are caused by plaque rupture
- B. Plaque rupture with mural thrombosis is also a common cause of episodic but asymptomatic progression to severe stenosis
- C. Of the coronary thrombi not caused by plaque rupture, most are caused by plaque erosion
- D. Plaque rupture is a more frequent cause of coronary thrombosis in men than in women
- E. All of the statements are true

32-4. Which of the following are characteristics of vulnerable plaques of the erosion-prone type?

- A. A plaque that contains a large and soft lipid-rich necrotic core
- B. A necrotic core covered by a thin and inflamed fibrous cap
- C. Big plaque size and expansive positive remodeling mitigating luminal obstruction
- D. Neovascularization (angiogenesis), plaque hemorrhage, and adventitial inflammation
- E. None of the above

32-5. Which of the following statements is *not true* regarding the fibrous cap in a fibroatheroma?

- A. The fibrocellular part of the plaque located between the necrotic core and the lumen is called the fibrous cap
- B. Assessed by microscopic examination postmortem, ruptured caps are typically < 65 μm thick
- C. In thin-cap fibroatheroma (TCFA), the necrotic core occupies > 50% of plaque area
- D. Thin fibrous caps are usually heavily inflamed, particularly those that have ruptured
- E. Apoptosis is common at the site of fibrous cap rupture

32-6. The coronary heart disease (CHD) risk equivalent concept includes all of the following *except*:

- A. Symptomatic disease in noncoronary arteries
- B. Carotid stenosis of > 50%
- C. Ankle-brachial blood pressure index < 0.8
- D. Abdominal aortic aneurysm
- E. Asymptomatic carotid bruit

32-7. Which of the following statements is *not true*?

- A. The total amount of CAC (usually expressed as the *Agatston score*) is a strong predictor of coronary events and provides prognostic information beyond that provided by traditional risk factor scoring
- B. Contrast-enhanced CT angiography visualizes not only the lumen but also the arterial wall
- C. Intravascular ultrasound (IVUS) can detect and localize plaque as well as quantitate plaque burden, but it requires selective catheterization and motorized pullback in the arteries of interest
- D. Serial examinations of well-defined coronary segments have been used to monitor the speed of plaque progression (or regression) over time in patients with established CHD
- E. Most acute coronary events originate from angiographically obstructive plaques

32-8. Which of the following is *not* a common characteristic of the TCFA?

- A. Large necrotic core
- B. Inflamed fibrous cap
- C. Uniform pattern of calcification
- D. Expansive remodeling
- E. Neovascularization

32-9. Which of the following statements is *not true* of coronary CT angiography?

- A. Coronary CT may visualize the lumen and detect obstructive and nonobstructive plaques
- B. Coronary CT may quantify calcified and noncalcified plaque burden
- C. Coronary CT may provide additional prognostic information by the detection of higher-risk plaques characterized by large plaque volume
- D. Coronary CT may provide additional prognostic information by the detection of higher-risk plaques characterized by high CT attenuation
- E. Coronary CT may provide additional prognostic information by the detection of higher-risk plaques characterized by the napkin-ring sign and expansive remodeling

32-10. Which of the following catheter-based technologies may have potential for the assessment of coronary atherosclerosis and vulnerable plaques?

- A. Conventional grayscale IVUS and virtual histology IVUS
- B. Coherence tomography and angioscopy
- C. Near-infrared spectroscopy
- D. Intracoronary magnetic resonance imaging and thermography
- E. All of the above

ANSWERS

32-1. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 32*) Causal and modifiable risk factors for atherosclerotic cardiovascular disease are well known (eg, smoking, dyslipidemia, high blood pressure, diabetes) and account for most (*not less than 50%*) of heart attacks in both sexes (option A).¹ However, for unknown reasons, the individual susceptibility to these risk factors varies greatly, and consequently, their predictive value is limited (option B).^{2,3} Most first heart attacks occur among people with average or only slightly elevated risk factor levels (option C).⁴⁻⁶ Recurrent events still occur despite lowering of these levels,^{7,8} indicating that we need both better detection and better treatment of those who are destined for a heart attack. Better detection of at-risk individuals may be achieved by visualizing the diseased arterial wall rather than just assessing risk factors (option D).

32-2. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 32*) Atherosclerosis is a chronic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development (option A),⁹⁻¹¹ predominantly at sites characterized by low and oscillatory (*not high and nonoscillatory*) endothelial shear stress (bifurcations, inner wall of curvatures) and preexisting intimal thickenings (option B).^{12,13} The speed of disease progression varies greatly, but it usually takes decades to develop the advanced atherosclerotic lesions responsible for clinical disease (option C). Plaques are very heterogeneous in size and composition, even plaques located next to each other and exposed for the same systemic risk

factors (option D). Most plaques remain asymptomatic (subclinical disease), some become obstructive (stable angina), and a few, if any, become vulnerable and lead to atherothrombotic events such as a fatal heart attack or a disabling stroke (option E).

- 32-3. The answer is A.** (Hurst's *The Heart*, 14th Edition, Chap. 32) The great majority of symptomatic coronary thrombi (~75%) (*not approximately 50%*) are caused by *plaque rupture* (option A).¹¹ Plaque rupture with mural thrombosis (with or without plaque hemorrhage) is also a common cause of episodic but asymptomatic progression to severe stenosis (option B).^{14,15} The remaining thrombi are caused by less well-defined mechanisms, of which so-called *plaque erosion* is the most common type (option C).¹¹ Plaque rupture is a more frequent cause of coronary thrombosis in men (~80%) than in women (~60%) but, except for sex and menopause, no other risk factors have consistently been connected with a particular mechanism of thrombosis (option D).¹¹ By inference, there are two major types of vulnerable plaques, rupture-prone and erosion-prone, that are presumed to look like the corresponding thrombosed plaques, just without rupture and thrombosis.¹⁶
- 32-4. The answer is E.** (Hurst's *The Heart*, 14th Edition, Chap. 32) All of the listed characteristics are properties of rupture-prone rather than erosion-prone plaques (option E). Vulnerable plaques of the erosion-prone type are heterogeneous and defined only by their fate (thrombosis, mostly mural).^{11,16} The surface endothelium is missing, but whether it vanished before or after thrombosis remains unknown. No distinct morphologic features have been identified, but in general, eroded plaques with thrombosis are scarcely calcified, rarely associated with expansive remodeling, and only sparsely inflamed.^{11,16} So, irrespective of plaque type, it is a misconception that vulnerable plaques are heavily inflamed. In contrast with the erosion-prone plaque, the prototype of a presumed rupture-prone plaque contains a large and soft lipid-rich necrotic core covered by a thin and inflamed fibrous cap.^{16,17} Associated features include big plaque size, expansive positive remodeling mitigating luminal obstruction (mild stenosis by angiography), neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a *spotty* pattern of calcifications. Although the macrophage density in ruptured caps is high,^{16,17} whole-plaque macrophage density rarely exceeds a small percent because ruptured caps are tiny.
- 32-5. The answer is C.** (Hurst's *The Heart*, 14th Edition, Chap. 32) The fibrocellular part of the plaque located between the necrotic core and the lumen is called the *fibrous cap* (option A). It is extremely thin in coronary plaque rupture.^{16,17} Assessed by microscopic examination postmortem, ruptured caps were usually < 65 μm thick (option B).¹⁸ Assessed by optical coherence tomography in vivo, the mean thickness was only 49 μm .¹⁹ If the fibrous cap is thin, the plaque is called a *thin-cap fibroatheroma* (TCFA).^{18,20} In TCFA, the necrotic core occupies approximately 23% of plaque area (*not more than 50%*) (option C).²⁰ Thin fibrous caps are usually heavily inflamed (macrophage density ~14%), particularly those that have ruptured (macrophage density ~26%) (option D),²⁰ but because they are thin, their ability to accommodate macrophages is limited. Apoptosis is common at the site of fibrous cap rupture, usually confined to macrophages because the vascular SMCs already have vanished when rupture occurs.^{20,21} With their ability to synthesize extracellular matrix, including collagen, SMC apoptosis is associated with impaired healing and repair, increasing the risk of plaque rupture.
- 32-6. The answer is C.** (Hurst's *The Heart*, 14th Edition, Chap. 32) Atherosclerosis is a generalized, multifocal arterial disease. However, compared with other arteries, the coronary arteries are in general the most susceptible to atherosclerosis and its thrombotic complications.^{22,23} Therefore, if atherosclerosis is present in noncoronary arteries, the coronary arteries will usually also be diseased, irrespective of symptoms.²⁴ The CHD risk equivalent concept introduced in the previous prevention guidelines included symptomatic disease in noncoronary arteries (option A), carotid stenosis of > 50% (option B), ankle-brachial blood pressure index < 0.9 (*not 0.8*) (option C), and abdominal aortic aneurysm (option D).²⁵ Asymptomatic carotid bruit is also associated with high CHD risk (option E).^{26,27}
- 32-7. The answer is E.** (Hurst's *The Heart*, 14th Edition, Chap. 32) The number and severity of stenoses determined by coronary angiography are signs of atherosclerosis with diagnostic, therapeutic, and prognostic implications.²⁸⁻³⁰ However, most acute coronary events originate from angiographically nonobstructive (*not obstructive*) plaques (option E), probably because they are much more numerous.^{17,16,31-34} An irregular lumen and/or filling defects indicating plaque disruption and/or thrombosis are associated with worse outcomes.³⁵ In contrast to coronary *luminography*, CAC detected by computed tomography (CT) imaging reveals the diseased arterial wall directly and correlates strongly with plaque burden.^{36,37} The total amount of CAC (usually expressed as the *Agatston score*) is a strong predictor of coronary events and provides prognostic information beyond that provided by traditional risk factor scoring (option A).³⁸ Contrast-enhanced CT angiography visualizes not only the lumen but also the arterial wall (option B). Because the strong relationship between the CAC score and coronary events is mediated predominantly by coexisting noncalcified or less calcified vulnerable plaques, total or noncalcified plaque burden detected by CT angiography may prove to be an even better marker of risk than the CAC score.^{39,40} Intravascular ultrasound (IVUS) can detect and localize plaque as well as quantitate plaque burden, but it requires selective catheterization and motorized pullback in the arteries of interest (option C). Serial examinations of well-defined coronary segments have been used to monitor the speed of plaque progression (or regression) over time in patients with established CHD (option D).⁴¹

- 32-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 32*) The TCFA has a distinct microstructure, including a large necrotic core (option A) covered by a thin and inflamed fibrous cap (option B), and other characteristic plaque features are common, such as a large, expansive remodeling (option D), neovascularization (angiogenesis) (option E), and a spotty (*not uniform*) pattern of calcification (option C).^{16,17}
- 32-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 32*) Coronary CT angiography may not only visualize the lumen and detect obstructive and nonobstructive plaques (option A), it may also quantify calcified and noncalcified plaque burden (option B). Furthermore, coronary CT angiography may also provide additional prognostic information by the detection of higher-risk plaques characterized by large plaque volume (option C), low (*not high*) CT attenuation (option D), napkin-ring sign, expansive remodeling (option E), and spotty calcification.^{42,43}
- 32-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 32*) Many catheter-based technologies have been developed or are under development for the assessment of coronary atherosclerosis and vulnerable plaques, including conventional grayscale IVUS, virtual histology IVUS (option A) and other ultrasound-based tissue characterization modalities, optical coherence tomography, angioscopy (option B), near-infrared spectroscopy (option C), intracoronary magnetic resonance imaging, thermography (option D), and vascular profiling.⁴⁴⁻⁴⁷ Because vulnerable coronary plaques of the rupture-prone type (TCFA) are relatively large, not numerous, and often cluster proximally in the major coronary arteries, their detection in patients undergoing percutaneous coronary interventions might be feasible.⁴⁸

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CHAPTER 33

Coronary Thrombosis: Local and Systemic Factors

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 33-1.** Initial atherosclerotic lesions result from the accumulation of inflammatory cells and lipids in which part or layer of the arterial wall?
- A. Arterial lumen
 - B. Intima
 - C. Media
 - D. Adventitia
 - E. All of the above
- 33-2.** Which of the following factors contributes to the attenuation of the proatherogenic state and lesion progression?
- A. Vascular cell adhesion molecule-1 (VCAM-1)
 - B. Matrix metalloproteinases (MMPs)
 - C. Elevated high-density lipoprotein (HDL)
 - D. Lipids at injury site
 - E. Interferon (IFN)-gamma
- 33-3.** Which of the following statements about the coagulation cascade is *correct*?
- A. Injury to vessel wall exposes subendothelial proteins such as collagen and von Willebrand factor (vWF) that can potentially activate platelets
 - B. Activated factor Xa is responsible for cleaving fibrinogen to fibrin, which forms a stable hemostatic plug over the injury site
 - C. Vitamin K is crucial for *de novo* synthesis of four clotting factors, including prothrombin
 - D. Platelets play an important role in coagulation via their ability to upregulate DNA replication following binding of tissue factor to their surface receptor
 - E. Upon stimulation, intracellular calcium blocks platelet degranulation, thereby inhibiting platelet activation
- 33-4.** Which of the following is an intrinsic mechanism developed to control coagulation reactions?
- A. Hemodilution of coagulation factors
 - B. Proteolytic feedback by thrombin
 - C. Protein C
 - D. Fibrinolysis
 - E. All of the above
- 33-5.** A 55-year-old female flight attendant with a history of hypertension and atrial fibrillation recently underwent coronary angioplasty, transient ischemic attack, and stenting in the setting of a troponin-positive acute coronary syndrome. Which antithrombotic therapy is recommended for this patient?
- A. Aspirin and prasugrel
 - B. Aspirin and warfarin
 - C. Aspirin and clopidogrel and warfarin
 - D. Clopidogrel and warfarin
 - E. Warfarin alone
- 33-6.** The P2Y and P2X receptors play an important role in platelet activation and thrombus formation. Which of the following statements about these receptors is *false*?

- A. P2Y₁ is responsible for platelet shape change and calcium mobilization
- B. P2X₁ is an ADP-gated calcium channel receptor involved in platelet shape change
- C. P2Y₁₂ is responsible for the platelet aggregation response to ADP
- D. P2Y₁ is responsible for TXA₂ generation
- E. cAMP is an important signaling molecule downstream of P2Y₁₂ activation

33-7. Which of the following statements about atherosclerotic plaque neovascularization is *correct*?

- A. Vasa vasorum in the intima spreads into the adventitia, where it prompts neovascularization and plaque growth
- B. Neovascularization is responsible for stabilizing and strengthening atherosclerotic plaques
- C. Promotion of plaque neovascularization is a potential therapeutic strategy to prevent plaque disruption
- D. Leaky vasa vasorum in the intima results in macrophage infiltration and plaque destabilization
- E. All of the above

33-8. The innate and acquired immune systems are important modulators of inflammation and atherosclerosis. Which of the following associations is *false*?

- A. Monocytes and Ly6C/GR-1
- B. Dendritic cells and CD4
- C. Platelets and CD40L
- D. T cells and CD8
- E. Mast cell and histamine

33-9. A 60-year-old man is rushed to the emergency room after sustaining a myocardial infarction (MI) during strenuous exercise. What is the *most likely* explanation for this patient's coronary thrombosis?

- A. An atherosclerotic plaque rupture led to exposure of subendothelial matrix elements and resulted in a persistent thrombotic occlusion and MI
- B. The ruptured plaque had a very small atheromatous core, which increased plaque thrombogenicity and risk of MI
- C. A residual mural thrombus resulted in a decreased shear rate, which facilitated the activation and deposition of platelets on the lesion
- D. Lack of macrophages in the atherosclerotic plaque led to activation of MMPs that resulted in plaque disruption and thrombus formation
- E. None of the above

33-10. A mother brings her 4-year-old daughter to the emergency room with a severe nosebleed. After careful examination and proper testing, she is diagnosed with von Willebrand disease, characterized by a missing or defective vWF. Given what is known about blood clotting, what step in the coagulation cascade is dysregulated in this disease?

- A. Proteolytic cleavage of prothrombin to thrombin
- B. Platelet degranulation
- C. Binding of TF to factor VII
- D. Platelet adhesion to injury site
- E. Binding of ADP to P2Y₁ receptor

ANSWERS

33-1. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 33*) Atherosclerosis is a systemic disease involving the intima of large and medium-sized arteries that is characterized by intimal thickening caused by the accumulation of cells and lipids (option B).¹ However, secondary changes may occur in the underlying media (option C) and adventitia (option D), particularly in advanced disease stages. The early atherosclerotic lesions might progress without compromising the lumen because of compensatory vascular enlargement (Glagovian remodeling) (option A).² Importantly, the culprit lesions leading to acute coronary syndromes are usually mildly stenotic and therefore barely detected by angiography.³ These high-risk, rupture-prone lesions usually have a large lipid core, a thin fibrous cap, and a high density of inflammatory cells.

33-2. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 33*) Inflammation is an important process that affects plaque progression, vulnerability, and subsequent thrombus formation. Inflammatory cells (monocyte/macrophages, T cells, and mast cells) present in the core and shoulder of atherosclerotic lesions release inflammatory cytokines and MMPs that affect each step of atherosclerosis from lesion formation, to progression, to disruption and ACS (option B). The circulating monocytes are recruited within the subendothelial space in response to the synthesis and exposure of adhesive proteins triggered by the early accumulation of lipids (option D). The internalized monocytes release inflammatory

mediators, such as netrin-1 and VCAM-1, that are responsible for their retention in the lesions (option A). Mast cells are proinflammatory through the release of histamine, leukotrienes, interleukin (IL)-6, and interferon (IFN)-gamma (option E). Attenuation of the proatherogenic state occurs through HDL-raising and may facilitate the efflux of the wall macrophages (option C).

- 33-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 33*) The coagulation cascade constitutes a series of molecules that interact with each other in a controlled manner to produce a rapid and amplified response to vessel wall injury. In the case of an atherosclerotic lesion, plaque rupture facilitates the interaction of the inner plaque components with the circulating blood.⁴ At the site of vascular lesion, circulating von Willebrand factor (vWF) binds to the exposed collagen that subsequently binds to the glycoprotein (GP) Ib/IX receptor on the platelet membrane (option A). Tissue factor (TF), another plaque component, exhibits a potent activating effect on platelets and coagulation. Platelet activation triggers intracellular signaling via second messengers, such as calcium, that induce shape change and secretion of their granular contents (option E). While platelets are nucleated cells that are devoid of genomic DNA, they contain messenger RNA and have the ability to synthesize proteins following activation (option D). Some clotting factors, namely factors VII, IX, X, and prothrombin, require vitamin K to undergo a posttranslational modification necessary for their ability to bind cell membrane surfaces. Without vitamin K, these factors can be synthesized but will not participate in proper clotting reactions (option C). Finally, clotting factors must be enzymatically cleaved in order to become active. Activated factor Xa is responsible for cleaving prothrombin to thrombin, which can then cleave fibrinogen to fibrin to form the hemostatic plug over the injury site (option B).
- 33-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 33*) Several mechanisms exist to control and limit coagulation reactions and maintain hemostasis. Coagulation is normally restricted to the site of injury by hemodilution of clotting elements, thereby limiting the size of the platelet plug and washing away coagulation factors as blood flows (option A). Although thrombin plays a pivotal role in maintaining the complex balance of initial prothrombotic reparative events, it also controls the subsequent anticoagulant and fibrinolytic pathways through proteolytic feedback mechanisms (option B). Thrombin has a specific receptor in endothelial cell surfaces, thrombomodulin, which triggers a physiologic anticoagulation system. Thrombin generated at the site of injury binds to thrombomodulin, and the complex serves as a receptor for the vitamin K-dependent protein C, which is activated and released from the endothelial cell surface. Activated protein C then inactivates factors Va and VIIIa and limits thrombin effects (option C). Fibrinolysis, the enzymatic breakdown of the fibrin clots, involves catalytic activation of zymogens, positive and negative feedback control, and inhibitor blockade (option D). Blood clotting is blocked at the level of the prothrombinase complex by the physiologic anticoagulant-activated protein C. Activated protein C cleaves factor Va, rendering it functionally inactive, thereby blocking thrombin formation.
- 33-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 33*) Patients presenting with troponin-positive acute coronary syndromes should be considered for treatment with dual antiplatelet therapy to reduce the risk of ischemic complications, irrespective of whether an intracoronary artery stent was used in the management of the patient. Patients treated with intracoronary stenting particularly should receive dual antiplatelet therapy to reduce the risk of stent thrombosis (option A). In addition, oral anticoagulants such as warfarin or NOACs are considered as part of "triple therapy" when an indication for antithrombotic therapy is present (eg, atrial fibrillation, venous thromboembolic disease) (option B). Although such triple therapy increases bleeding risk, this is the current standard of care, although several ongoing clinical trials are examining alternative regimens (options C, D, and E).
- 33-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 33*) Great interest in the platelet ADP receptors (P2Y, P2X) has recently been generated because of available pharmacologic inhibitors. The P2Y₁ receptor is responsible for inositol trisphosphate formation through the activation of phospholipase C, leading to transient increase in the concentration of intracellular calcium, platelet shape change, and weak transient platelet aggregation (option A).^{5,6} Pharmacologic data have also revealed an essential role for the P2Y₁ receptor in the initiation of platelet ADP-induced activation, TXA₂ generation, and platelet activation in response to other agonists (option D). The P2Y₁₂ receptor is responsible for completion of the platelet aggregation response to ADP (option C), and it has several important downstream signaling molecules, including cAMP (option E). Pharmacologic approaches have shown a role for the P2Y₁₂ receptor in dense granule secretion, fibrinogen-receptor activation, P-selectin expression, and thrombus formation. Although not activated by ADP, platelets possess a third purinergic receptor (P2X₁), which is a fast adenosine triphosphate (ATP)-gated calcium channel receptor mainly involved in platelet shape change.
- 33-7. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 33*) Recent evidence has highlighted the importance of lesion neovascularization in plaque destabilization and plaque growth.⁷⁻⁹ Preexisting vasa vasorum in the adventitia is thought to spread into the intima, prompting intimal neovascularization (option A).⁸ Leaky vasa vasorum with the subsequent red blood cell extravasation is thought to be a major source of macrophage infiltration, and it increases the vulnerability of the atherosclerotic lesions (option D). A recent study using optical coherence tomography has associated vasa vasorum increase with fibrous plaque volume and intraplaque neovessels with plaque vulnerability (option B).¹⁰ Inhibition of plaque neovascularization could thus be seen as a potential new therapeutic intervention to prevent plaque disruption (option C).
- 33-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 33*) Monocytes, dendritic cells, and mast cells are the major

players in innate immunity (Figure 33-1). Mast cells are inflammatory by releasing histamine, leukotrienes, interleukin (IL)-6, and interferon (IFN)-gamma (option E). Dendritic cells are responsible for antigen presentation via human leukocyte antigen (HLA) molecules CD80/86 and CD40 (option B). Monocytes are divided into two major types according to their expression of CD14 and CD16, and can be further classified by their expression of the proinflammatory molecule Ly6C/GR-1 (option A). Platelets also play an important role in the inflammatory environment by secreting various vasoactive chemokines and cytokines such as CD40L (option C). Finally, T cells of the acquired immunity are either CD4⁺ or CD8⁺ and likewise play a crucial role in the destabilization of atherosclerotic lesions (option D).






Monocytes		Dendritic cells	Mast cells	Activated platelets
				
Ly6C/GR-1 positive TLRs Proteases Redox species TNF IL-1 Cytokines	Ly6C/GR-1 negative TGF-β CD36 SR-A CD163 VEGF	HLA molecules CD80/86 CD40	Histamine Leukotrienes Chymase IL-6 Interferon	CD40L RANTES MRP-8/14 PDGF TGF-β
Pro-inflammatory		Anti-inflammatory?	Antigen presentation	Inflammatory
				Hemostasis

FIGURE 33-1 Major cell players involved in innate immunity.

- 33-9. The answer is A.** (*Hurst’s The Heart, 14th Edition, Chap. 33*) The mechanisms of platelet deposition and thrombus formation after vascular damage are modulated by the type of injury, the local geometry, and local hemodynamic conditions.^{11,12} Tissue factor (TF) readily available in the atherosclerotic intimal space exposed by endothelial loss contributes to the high thrombogenicity of atherosclerotic plaques.^{13,14} As such, when injury to the vessel wall is mild, the thrombogenic stimulus is relatively limited, and the resulting thrombotic occlusion is transient, as occurs in UA. On the other hand, deep vessel injury secondary to plaque rupture or ulceration results in exposure of collagen, TF, and other elements of the vessel matrix, leading to relatively persistent thrombotic occlusion and MI (option A). Studies show that the atheromatous core is up to sixfold more active than the other plaque substrates in triggering thrombosis.¹¹ Therefore, ruptured plaques with a large atheromatous core are at high risk of leading to ACS (option B). Macrophages are suggested to play a key role in inducing plaque rupture by secreting proteases capable of destroying the ECM that provides physical strength to the fibrous cap. Recently, it has been shown that macrophage-mediated matrix degradation by MMPs can induce plaque rupture (option D). Additionally, because platelet deposition increases with increasing degrees of vessel stenosis, residual mural thrombus encroaching into the vessel lumen may result in an increased shear rate, which facilitates the activation and deposition of platelets on the lesion (option C).
- 33-10. The answer is D.** (*Hurst’s The Heart, 14th Edition, Chap. 33*) Von Willebrand factor (vWF) is an important clotting factor present in blood plasma, endothelium, and subendothelial connective tissue. Its primary function is binding to other proteins and stimulating platelet adhesion to wound sites (option D). At the site of vascular lesions, circulating vWF binds to the exposed collagen that subsequently binds to the glycoprotein (GP) Ib/IX receptor on the platelet membrane. Under pathological conditions and in response to changes in shear stress, vWF can be secreted from the storage organelles in platelets or endothelial cells, reinforcing the activation process. vWF is not an enzyme, and thus it has no catalytic activity or effect on the conversion of prothrombin to thrombin (option A). Platelet activation by various agonists, such as ADP, leads to the mobilization of calcium and subsequent release of its granular content (option B). Likewise, vWF is not responsible for TF binding to factor VII, which happens physiologically or pathologically following exposure of TF during injury (option C). vWF is also not required for the binding of the ADP agonist to its receptor, P2Y₁ (option E). [Figure 33-2](#) highlights the mechanisms involved in platelet adhesion, activation, and aggregation.

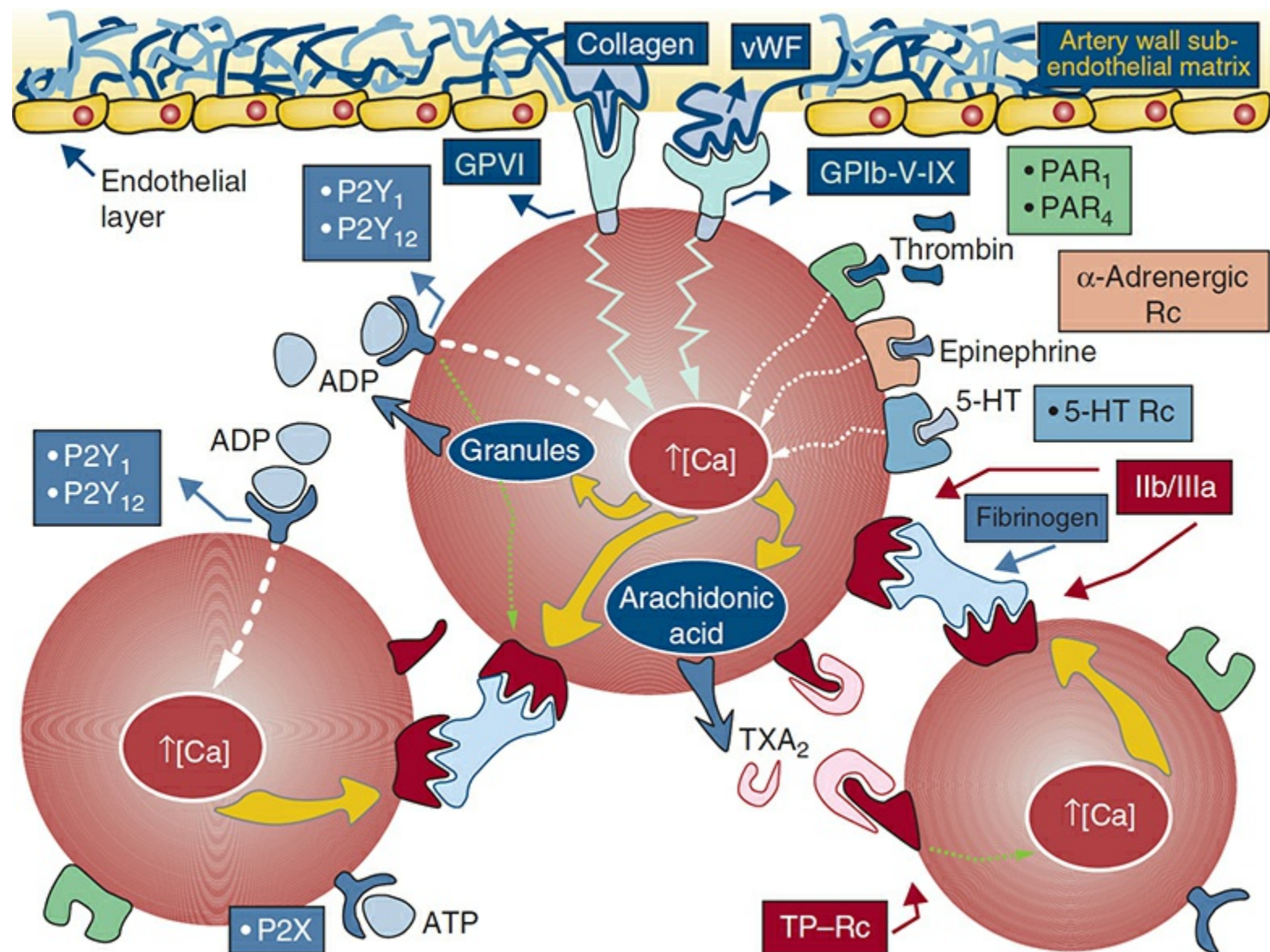


FIGURE 33-2 Mechanisms and agonists involved in platelet adhesion, activation, and aggregation. (Reproduced with permission from Ibanez B, Vilahur G, Badimon J. Pharmacology of thienopyridines: rationale for dual pathway inhibition, *Eur Heart J Suppl.* 2006;8(Suppl G):G3-G9.)

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CHAPTER 34

Coronary Blood Flow and Myocardial Ischemia

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

34-1. Which of the following statements about myocardial ischemia is *true*?

- A. Elective revascularization trials driven by ischemia on diagnostic testing has not yet been shown to reduce myocardial infarction despite relief of angina
- B. Revascularization of routinely identified coronary stenoses can improve mortality
- C. Revascularization is more effective than medical treatment in preventing myocardial infarction and coronary death in stable CAD
- D. Immediate percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS) fails to reduce the risk of subsequent myocardial infarction
- E. All of the above

34-2. A 66-year-old man undergoes exercise testing with myocardial perfusion imaging. What effect will dipyridamole administration have on this patient in the presence of a 95% diameter stenosis in a coronary artery?

- A. It will cause progressive coronary narrowing, reducing coronary flow reserve (CFR) but not resting flow
- B. A fall in coronary perfusion pressure due to a steal phenomenon and associated subendocardial ischemia
- C. Coronary control mechanisms will be activated and will prevent the invocation of maximal vasodilatory capacity
- D. Vasodilator-mediated increased coronary flow will cause a rise in coronary perfusion pressure to the epicardium
- E. None of the above are correct

34-3. In a fluid dynamic model of stenosis and diffuse narrowing, what is the relationship between arterial radius and coronary flow?

- A. Coronary flow is directly proportional to arterial radius
- B. Coronary flow is inversely proportional to arterial radius
- C. Coronary flow is proportional to the arterial radius divided by four
- D. Coronary flow is proportional to the arterial radius raised to the fourth power
- E. Coronary flow is independent of arterial radius

34-4. Which of the following statements about coronary blood flow in women is *correct*?

- A. Women have larger coronary arteries and higher myocardial perfusion
- B. Women have low endothelial shear, which reduces “leaky” endothelial cell junctions
- C. Women have high endothelial shear that promotes atheroma formation
- D. Women can have high endothelial shear that inhibits low-density lipoprotein transport
- E. Women upregulate endothelial NADPH oxidase, thereby increasing oxidative stress

34-5. Which of the following accurately describes the difference in blood flow through a nonstenotic artery compared with a stenotic artery?

- A. A stenosis imposes an area of low wall pressure
- B. Flow velocity is greater through a nonstenotic section of an artery
- C. A section of nonstenosis is an area of high endothelial shear
- D. High endothelial shear stress is atherogenic
- E. The viscous pressure loss across a stenosis is linearly proportional to flow squared

34-6. Which of the following is *true* about myocardial steal and its mechanisms?

- A. Intramyocardial steal refers to blood flow being withdrawn from the subendocardium by the subepicardium

- B. As flow increases through a stenosis, the pressure gradient increases, and distal coronary pressure falls
- C. Pharmacological vasodilators increase epicardial flow, thereby decreasing the pressure gradient across the stenosis
- D. It manifests as stress-induced ST elevations on ECG and angina with reduced average transmural perfusion
- E. All of the above

34-7. Which of the following mechanisms regulating coronary blood flow is *incorrect*?

- A. Metabolic demand is the primary controller of coronary blood flow
- B. Both sympathetic and parasympathetic neurons enervate the coronary arteries
- C. Increased coronary blood flow increases endothelial shear and results in vasodilation
- D. A sudden rise in coronary pressure results in a sustained increase in coronary blood flow
- E. All of the above are incorrect

ANSWERS

34-1. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 34*) Immediate PCI in ACS reduces the risk of recurrent myocardial infarction (option D). However, elective revascularization trials driven by "ischemia" on diagnostic testing has not yet been shown to reduce myocardial infarction or cardiovascular deaths despite relief of angina (option A; not option B). In addition, the failure of randomized revascularization trials to reduce myocardial infarction or coronary deaths compared to medical treatment alone in "stable CAD" has been demonstrated in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial¹ (option C).

34-2. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 34*) Experimentally and clinically, maximal hyperemic flow for determining CFR is achieved pharmacologically by arteriolar vasodilating drugs such as dipyridamole, adenosine, and regadenoson. Progressive coronary narrowing reduces CFR with little change in resting flow until an approximately 80% to 90% diameter stenosis. At these levels of severe stenosis, resting blood flow falls (option A), but some residual CFR capacity remains upon pharmacologic vasodilator stimulus. Stenosis severe enough to reduce resting perfusion does not elicit all remaining reserve vasodilator capacity because of a self-regulating mechanism that protects subendocardial perfusion. At such severe stenosis reducing resting perfusion, any increase in vasodilator-mediated increased coronary flow causes a proportionately greater fall in coronary perfusion pressure, thereby reducing subendocardial perfusion more than subepicardial perfusion, and causing subendocardial (option D is incorrect) ischemia, angina, and ST depression on ECG. When exercise or pharmacologic vasodilation forces greater vasodilation than stable resting conditions, this protective control is overridden (option C), with ensuing subendocardial ischemia (option B).

34-3. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 34*) The relationship between arterial radius and coronary flow is depicted in Figure 34-1. Coronary flow is a function of the arterial radius raised to the fourth power (option D).

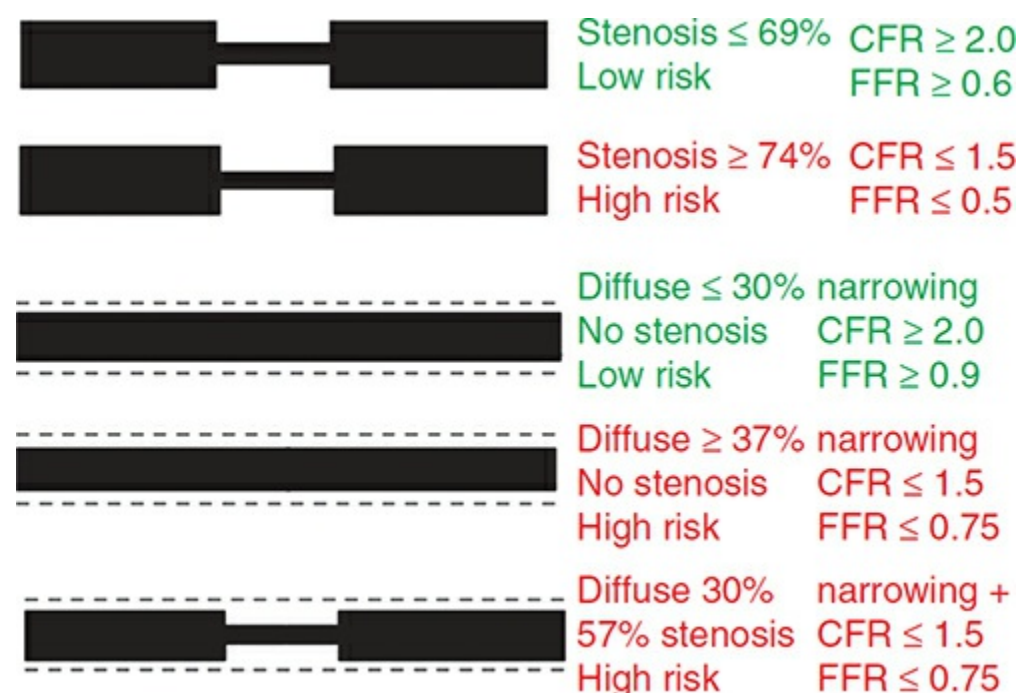


FIGURE 34-1 Computer models of stenosis and calculated coronary flow reserve (CFR) and fractional flow reserve (FFR) based on fluid dynamic analysis of the entire branching coronary artery tree with and without stenosis or diffuse narrowing. (Reproduced with permission from Gould KL, Johnson NP, Kaul S, et al. Patient selection for elective revascularization to reduce myocardial infarction and mortality: New lessons from randomized trials, coronary physiology, and statistics, *Circ Cardiovasc Imaging* 2015 May;8(5). pii: e003099.)

34-4. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 34*) CAD in women is characterized by atypical chest pain, diffuse epicardial coronary atherosclerosis, microvascular dysfunction, inaccurate diagnostic tests, delayed or late ACS associated with high mortality, and differential responses to medical treatment or invasive procedures in women

compared to men. Coronary arteries in women are smaller than in men (option A), but myocardial perfusion is higher in women. Accordingly, average endothelial shear is higher in women. High endothelial shear stress inhibits low-density lipoprotein transport (option D) by reducing “leaky” endothelial cell junctions (option B); inhibiting inflammation, platelet activation, and thrombosis; retarding oxidative processes; promoting mild stable uniform remodeling; and inhibiting focal atheroma (option C), focal stenosis, and plaque instability. These beneficial effects are mediated by high shear that upregulates endothelial nitric oxide (NO), NO synthase (eNOS) gene expression, eNOS phosphorylation, and manganese superoxide dismutase (Mn-SOD) expression and downregulates endothelial NADPH oxidase, thereby decreasing superoxide ion and oxidative stress (option E).

34-5. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 34*) Figure 34-2 shows the fluid dynamic equations relating stenosis dimensions, coronary blood flow, pressure gradient, flow profiles, exit vortex shedding, and endothelial shear stress. A normal nonstenotic artery is defined by low flow velocity (option B), high pressure and low shear (option C). Meanwhile, a stenotic artery is defined by high flow velocity, low pressure, and high shear (option A). The quadratic equation has a viscous pressure loss linearly proportional to flow (option E) and an exit separation loss proportional to flow squared. Both viscous and separation pressure losses are related to the arterial radius raised to the fourth power. Consequently, small changes in arterial diameter that are not visible or quantifiable on angiogram may have major effects on coronary flow or CFR, incurring high or low risk. High endothelial shear stress has antiatherogenic effects, whereas low shear stress is atherogenic (option D), with implications for the different manifestations of CAD in women versus men.

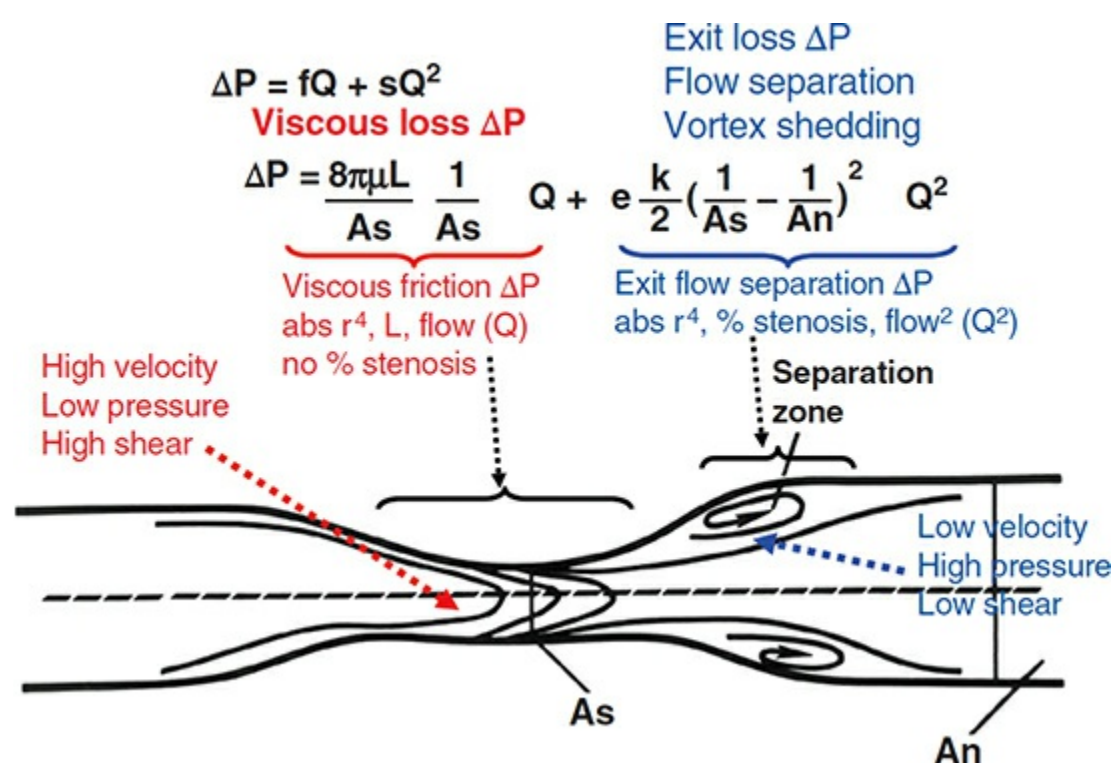


FIGURE 34-2 Schema of blood flow through a stenosis with fluid dynamic equation characterizing stenosis severity.

Abbreviations: μ , blood viscosity; ΔP , pressure gradient across the stenosis; A_n , cross-sectional area of the normal nonstenotic artery; A_s , cross-sectional lumen area of the stenosis; k , constant; L , stenosis length; ΔP , pressure gradient; Q , flow; fQ , friction coefficient of flow; sQ , separation coefficient of flow squared.

34-6. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 34*) Intramyocardial steal, also called subendocardial-subepicardial steal, manifests as stress-induced ST depression on ECG and usually angina with reduced average transmural perfusion in cc/min/g to the ischemic threshold of 0.9 cc/min/g (option D). As flow increases through a stenosis, the pressure gradient increases, and distal coronary pressure falls (option B), thereby impairing subendocardial perfusion more than the subepicardium. This subepicardial to subendocardial perfusion gradient is called intramyocardial steal because of the superficial appearance of perfusion being “stolen away” from the subendocardium by the subepicardium (option A). As epicardial perfusion pressure and flow fall because of stenosis, the subendocardium vasodilates maximally as a result of ATP release from red blood cells that prevents ischemia up to a limit. At that level of epicardial perfusion pressure and flow, the subepicardium sees higher pressure and flow, thereby not vasodilating maximally. With added pharmacologic vasodilator stress, the epicardial flow increases, the pressure gradient across the stenosis increases (option C), and perfusion pressure falls, thereby making the subendocardium ischemic.

34-7. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 34*) Of the many factors affecting coronary blood flow, the primary controller is metabolic demand (option A) that nearly instantaneously regulates regional coronary flow, even in small separate myocardial regions independently. Myocardial oxygen demand regulates coronary blood flow via ATP release from oxygenated red blood cells at low myocardial pO_2 . Coronary arterial smooth muscle inherently responds to changes in arterial pressure even with adequate arterial oxygenation and in the absence of myocardium or neural connections. A sudden rise in coronary pressure that initially increases coronary blood flow incurs coronary artery vasoconstriction that reduces flow back toward baseline (option E). Both sympathetic and parasympathetic neural networks enervate the coronary arteries (option B). The direct neural effect of parasympathetic stimulation is coronary vasodilation that would increase coronary blood, while the direct neural effect of beta-sympathetic blockade causes coronary vasoconstriction. As a component of its complex molecular biology, arteriolar vasodilation with increased coronary blood flow also increases endothelial shear stress that normally triggers epicardial coronary artery vasodilation mediated by NO (option C). However, with endothelial dysfunction, shear-induced epicardial vasodilation is lost, or

vasoconstriction occurs.

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CHAPTER 35

Nonobstructive Atherosclerotic and Nonatherosclerotic Coronary Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 35-1.** Which of the following statements about normal coronary physiology and function is *correct*?
- A. Conductance and flow in the coronary microcirculation are governed by Poiseuille's law
 - B. Resistance in the conductive vessels of the precapillary coronary tree is primarily responsive to metabolic stimuli
 - C. Epicardial vessels represent the predominant resistance within the coronary flow circuit
 - D. All of the above
 - E. None of the above
- 35-2.** A 45-year-old woman presents to clinic with chest pain and shortness of breath. She had revascularization performed in the past, but her latest angiography results did not demonstrate residual obstructive epicardial coronary stenoses. Which of the following is *correct* about nonobstructive coronary artery disease (CAD)?
- A. Nonobstructive CAD is diagnosed much more often in men than in women
 - B. Results from noninvasive stress testing will likely be normal
 - C. The patient likely has preserved LV systolic function
 - D. All of the above are correct
 - E. None of the above are correct
- 35-3.** A 45-year-old female patient is evaluated for the presence of coronary microvascular dysfunction (CMD). Which of the following measurement techniques and expected outcomes is *not* correct?
- A. Administration of adenosine results in smooth muscle relaxation
 - B. Regadenoson is associated with a reduced risk of bradycardia and bronchoconstriction compared with adenosine
 - C. Invasive Doppler flow wire can measure coronary blood flow velocity and pressures
 - D. Acetylcholine has direct effects on smooth muscle relaxation and vasodilation
 - E. Adenosine has both endothelium-dependent and endothelium-independent effects on smooth muscle cells
- 35-4.** A 65-year-old man complains of new onset dyspnea and presyncopal episodes. He previously underwent heart transplantation six years ago for idiopathic dilated cardiomyopathy. Following a stress test and coronary CT, the patient is diagnosed with cardiac allograft vasculopathy (CAV) with diffuse narrowing of the coronary arteries. Which of the following is expected to be of limited efficacy in this patient without focal stenosis?
- A. Repeat heart transplantation
 - B. Statin
 - C. Percutaneous coronary intervention (PCI)
 - D. Calcium channel blocker
 - E. ACE inhibitors
- 35-5.** Which of the following statements about vasculitides that manifest with coronary arteritis is *correct*?
- A. Kawasaki disease affects medium arteries and can result in coronary artery aneurysms
 - B. Takayasu's arteritis is an autoimmune process affecting the vasa vasorum of large vessels
 - C. ANCA-associated vasculitides can manifest with myocardial scarring
 - D. Giant cell arteritis (GCA) may present initially with coronary manifestations
 - E. All of the above

- 35-6.** A 43-year-old man presents to the emergency room with anginal symptoms. Coronary angiography demonstrates patent coronary arteries, however, a tunneled (bridging) LAD artery is present. Which of the following could account for this patient's symptoms?
- A. The tunneled artery is surrounded by epicardial fat, which compresses the lumen and limits blood flow
 - B. Compression of the tunneled artery occurs during diastole because myocardial blood flow occurs predominantly during systole
 - C. The tunneled artery runs deep in the myocardium, creating a greater myocardial bridge and accounting for greater compression of the vessel lumen
 - D. Greater myocardial demand results in increased blood flow during diastole because systole is limited by the increase in heart rate
 - E. None of the above; a tunneled artery cannot account for this patient's symptoms
- 35-7.** A 43 year old man presents to clinic with exertional dyspnea and is found to be in clinical heart failure. Angiography revealed a fistula between the LAD and the pulmonary artery. What is the *most* appropriate treatment for this patient?
- A. Interventional (transcatheter) closure of the fistula
 - B. Beta-blocking agent
 - C. ACE inhibitor
 - D. Observation and continued follow-up
 - E. Answers B and C
- 35-8.** Which of the following statements about the pathophysiology of aneurysms is *correct*?
- A. The most common cause of aneurysms is dilatation secondary to vessel trauma
 - B. Dilatation involves the entire vessel wall (intima, media, and adventitia)
 - C. Aneurysms are often symptomatic and are discovered following patients' complaints
 - D. A "giant" aneurysm is defined as one having a dilatation diameter > 10 mm
 - E. All of the above are correct
- 35-9.** A 36-year-old woman presents to the emergency room with chest pains, which started 5 days after delivering her child. A coronary angiography revealed a retrograde dissection of the LAD. Which of the following is *true* regarding this patient's condition?
- A. Retrograde dissections should be treated surgically to prevent ischemic complications
 - B. Pregnancy is unrelated to the coronary dissection
 - C. Dissections always occur secondary to a triggering event, such as blunt force trauma
 - D. Coronary dissections are not associated with ischemic ECG changes
 - E. Retrograde dissections can be treated conservatively without further investigation
- 35-10.** Which of the following characteristics appropriately defines epicardial coronary spasms?
- A. Symptoms of angina pectoris occurring at rest
 - B. ST-segment changes on ECG
 - C. Minor elevations in serum C-reactive protein
 - D. Younger age and female predominance
 - E. All of the above are correct

ANSWERS

- 35-1. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 35*) Vessels branch and decrease in size, from prearterioles to arterioles to capillaries. Myocardial blood flow is regulated mostly in the coronary microcirculation, where only small changes in arteriolar diameter can result in large changes in conductance and flow as predicted by Poiseuille's law (option A). Despite a historical focus on the epicardial coronary macrovessels, the microvessels represent the predominant resistance within the coronary flow circuit (option C), and they are innumerable in comparison to the epicardial vessels seen during invasive coronary angiography. The precapillary coronary tree consists of conductive, prearteriolar, and arteriolar vessels. Resistance in these vessel components is primarily responsive to flow, pressure, and metabolic stimuli, respectively (option B) ([Figure 35-1](#)).

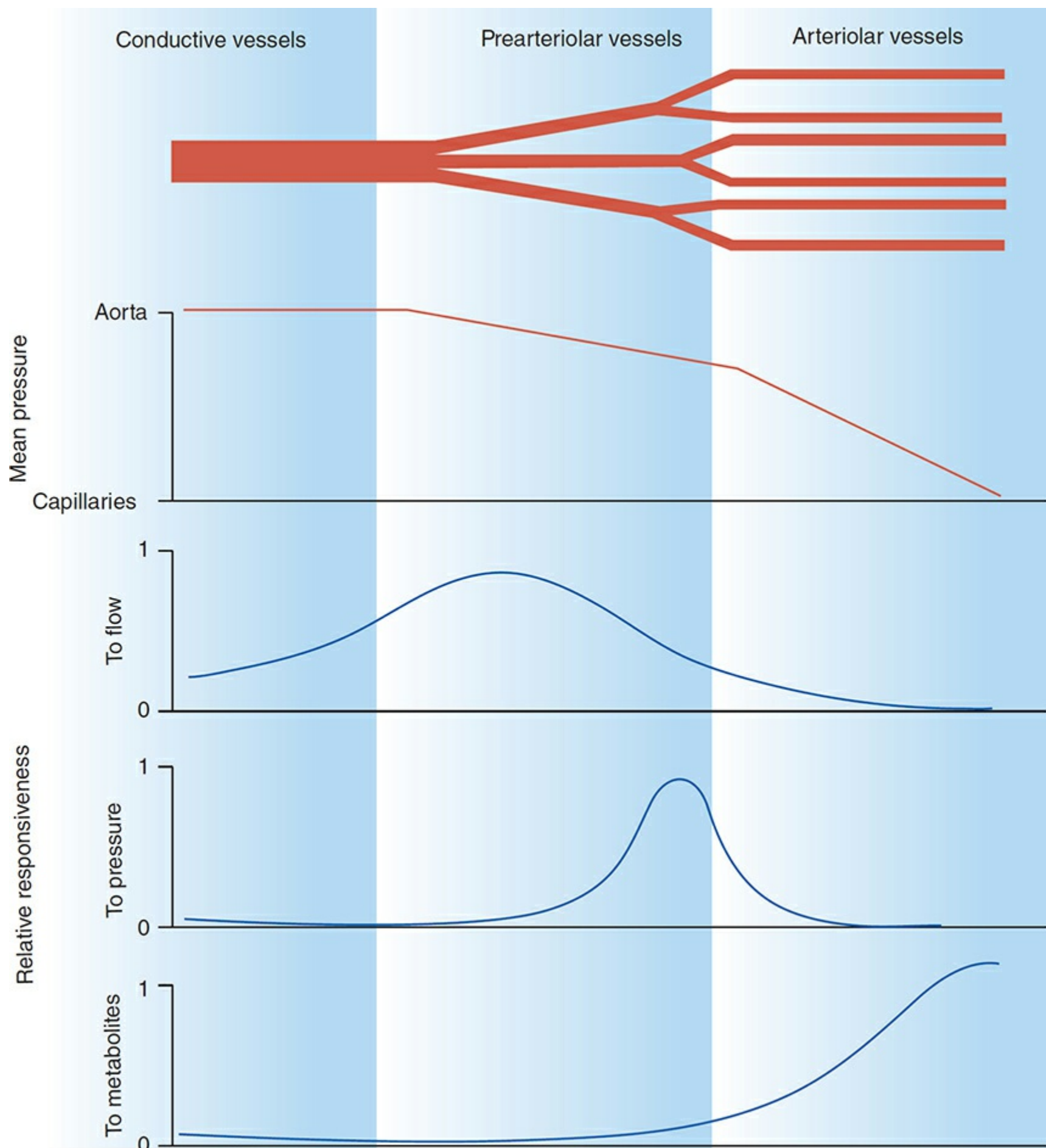


FIGURE 35-1 Components of the coronary circulation. (Reproduced with permission from Maseri A. *Ischemic Heart Disease*. New York: Churchill Livingstone; 1995.)

35-2. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 35*) A nontrivial proportion of patients with anginal symptoms and ischemia on stress testing (option B) have been noted to have an absence of fixed epicardial coronary arterial stenosis on coronary angiography.¹ The condition of angina with normal angiography, more accurately termed nonobstructive CAD, is being increasingly observed and is significantly more prevalent among women than men (option A).² In addition to those without fixed obstructive coronary stenosis, contemporary data suggest that 20% to 30% of patients with angina remain symptomatic despite technically successful revascularization and resolution of fixed epicardial coronary stenosis. In large international registries of patients referred for coronary angiography, the prevalence of nonobstructive CAD in women with angina symptoms may be as high as 65%.³ Even in the presence of preserved LV systolic function (option C), patients with nonobstructive CAD are at elevated long-term risk when compared to healthy cohorts.

35-3. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 35*) To evaluate for the presence of CMD, several provocative agents are dependent on functional endothelium, whereas others act directly on vascular smooth muscle and are considered endothelium-independent. The most commonly used pharmacological agent for endothelium-dependent testing is acetylcholine. In normal coronary arteries, acetylcholine releases nitric oxide (NO) from endothelium, overriding its direct effects at the vascular smooth muscle muscarinic receptor to induce vascular smooth muscle contraction, resulting in vasodilation. In arteries with dysfunctional endothelium, insufficient biologically active NO is released in response to acetylcholine, the drug's direct effect to activate vascular smooth muscle predominates, and

vasoconstriction occurs (option D). Adenosine is the most commonly used endothelium-independent pharmacological agent. Activation of adenosine A_{2A} receptors on vascular smooth muscle results in reproducible smooth muscle relaxation (option A). Regadenoson is a selective A_{2A} adenosine receptor agonist also used in pharmacologic stress testing because of reduced side effects (eg, less bradycardia and less bronchoconstriction) (option B). Adenosine receptors are also present in endothelium. As much as 25% of the hyperemic response obtained with intravenous adenosine infusion is the result of endothelial-dependent vasodilation (option E) because it can be blocked by infusion of NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase.⁴ Invasive measurement of coronary blood flow and CFR is predominantly performed using an intracoronary Doppler flow wire.⁵ The wire directly measures coronary blood flow velocity and can be combined with a pressure sensor (option C).

- 35-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 35*) CAV is a process whereby the allograft coronary arteries become diffusely and circumferentially narrowed with progressive luminal loss. CAV has few therapeutic options, with repeat transplantation being the only definitive treatment (option A). Statins (option B), calcium antagonists (option D), and angiotensin-converting enzyme inhibitors (option E) have all demonstrated some effect at reducing CAV.⁶ Some immunomodulating drugs may be more effective than others at slowing progression. Percutaneous coronary intervention is an option for focal stenoses in patients with advanced disease and compromised ventricular function but is not feasible for diffuse narrowing (option C). Antiplatelet agents may be given to reduce the risk of myocardial infarction, although the evidence supporting this is limited.
- 35-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 35*) The coronary arteries can be affected by systemic inflammatory conditions. Kawasaki disease is a childhood vasculitis that can manifest with coronary abnormalities. Widespread inflammation of medium-sized arteries results in coronary artery aneurysms (option A) in approximately 25% to 30% of patients who are not treated early. The mainstays of treatment are intravenous immune globulin and aspirin. The pathological cause of Takayasu's arteritis is not precisely known, but it is widely thought to result from an autoimmune process mediated by T cells and to affect the vasa vasorum of large vessels with leukocyte infiltration (option B). The ANCA-associated diseases most commonly affect the kidneys, lungs, eyes, nerves, and skin, and cardiac involvement may not be considered part of the typical presentation. However, up to half of patients may have cardiac abnormalities, and cardiac MRI often demonstrates myocardial scarring (option C).^{7,8} Giant cell arteritis is a vasculitis predominantly of older patients. Infiltration of the intima with giant cells can result in granuloma formation and thickening of the internal elastic lamina. In rare cases, GCA may present initially with coronary manifestations (option D).
- 35-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 35*) Occasionally, coronary artery segments of varying lengths may travel within the myocardium and reappear on the epicardium more distally in the arterial course. This is sometimes referred to as a *tunneled artery*, but the clinical phenomenon is most often referred to as the description of the overlying muscle, a *myocardial bridge*. On pathological specimens, the coronary artery is surrounded, not by epicardial fat, but by myocardium (option A). The degree of bridging and compression of the vessel lumen is variable, possibly relating to the varying depth of the tunneled segment within myocardium, with thicker myocardial bridges being potentially more symptomatic (*Figure 35-2*) (option C). Conceptually, the compression of a tunneled artery should be limited mostly to myocardial systole because coronary blood flow occurs predominantly during diastole. However, many bridges also restrict expansion of the coronary artery in diastole (option B). Additionally, augmentation of coronary blood flow required to meet increasing demands, such as exercise, is often accompanied by an increase in flow during systole because diastole is progressively limited by the increase in heart rate (option D). Thus ischemia, myocardial infarction, arrhythmias, and sudden death have all been attributed to myocardial bridging (option E).

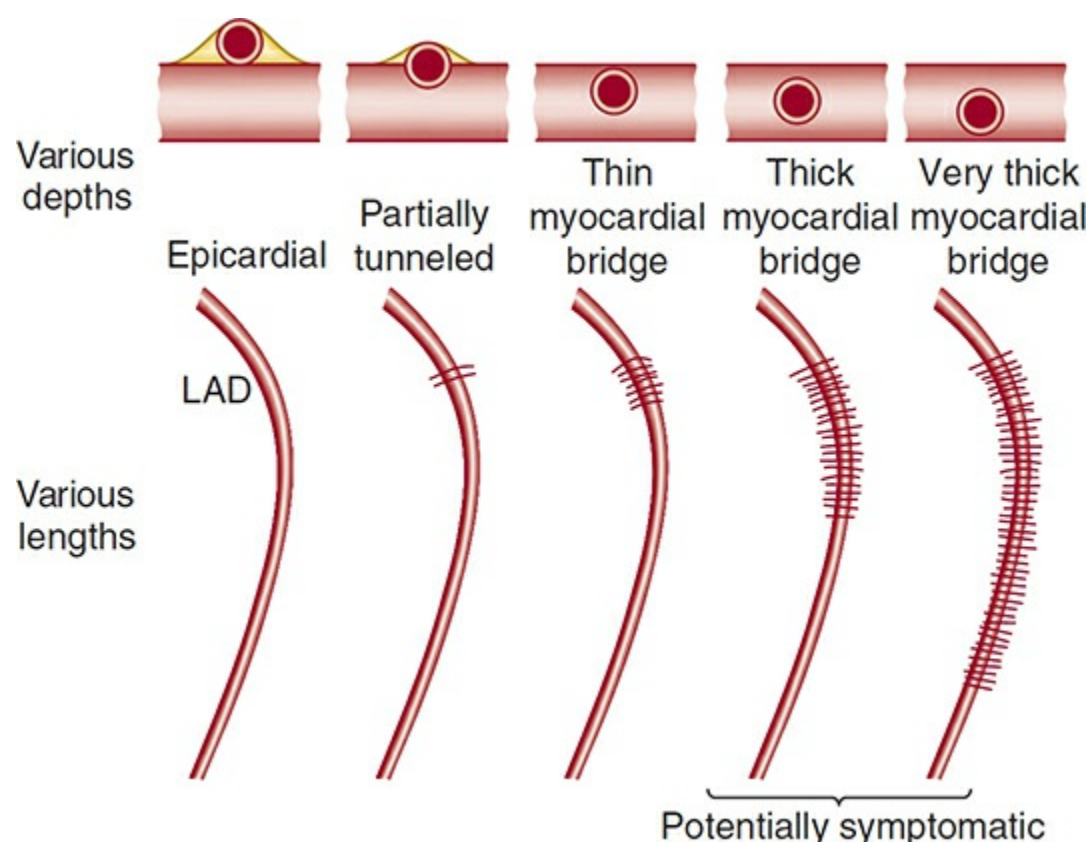


FIGURE 35-2 Diagram of myocardial bridging showing morphologic variations in tunneling (length of tunneled segment, depth

of tunneled segment). (Reproduced with permission from Pepine CJ. *Acute Myocardial Infarction*. Philadelphia: FA Davis; 1989.)

- 35-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 35*) An abnormal communication between an epicardial coronary artery and a cardiac chamber, major vessel (vena cava, subpulmonary veins, pulmonary artery), or other vascular structure (mediastinal vessels, coronary sinus) is known as a coronary artery fistula. Fistulas that connect the left circulation to left-sided chambers may not result in clinical disease and may be incidentally found on angiography. Fistulas between the left and right circulation result in a shunt of blood flow, which may be clinically relevant, depending on the volume of flow. Fistulas predispose to endocarditis and may present with continuous murmur, myocardial ischemia/angina, acute myocardial infarction, sudden death, coronary steal, congestive heart failure, arrhythmias, or coronary aneurysm formation.⁹ If patients present with heart failure or ischemia symptoms, the traditional evaluation often includes coronary angiography, which is the most reliable method of detecting coronary fistulas. Patients with incidentally found, asymptomatic, left-to-left fistulas can be managed conservatively (eg, with beta-blockers) and will often remain stable and symptom-free for long periods of time. Interventional occlusion or surgical repair (option A) is indicated for patients with symptoms attributable to the fistula or heart failure/cardiac remodeling caused by shunting of blood.
- 35-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 35*) An aneurysm of the coronary artery is a pathological dilation of the entire vessel wall: intima, media, and adventitia (option B). "Giant" aneurysms are often defined as those with diameters more than four times the normal diameter (option D), but dilations of 20, 30, and 40 mm are not uncommon. Aneurysms are present in about 1% of people at autopsy; the most common (up to 50% of cases) etiology is dilation secondary to vessel damage from atherosclerosis (option A). The malformation can be congenital or acquired secondary to atherosclerosis, trauma (external or iatrogenic), or inflammatory illnesses. Aneurysms are typically asymptomatic (option C) and are sometimes incidentally found on CT, angiography or, rarely, on echocardiography.
- 35-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 35*) Dissection refers to the separation of arterial wall layers and can occur spontaneously or as a secondary event (option C). Depending on the nature and severity of the dissection, the false lumen can compress or occlude the true lumen, resulting in ischemia, infarction, or death. Spontaneous or primary dissections are less common than secondary and are most commonly reported in young women, often associated with pregnancy (option B). Vessels can dissect in antegrade (toward the distal vessel) or retrograde (toward the vessel origin) patterns. The signs and symptoms of dissection are similar to ACS resulting from atherosclerotic disease: chest pain, ischemic ECG changes (option D), and elevated cardiac biomarkers. Antegrade dissections are often treated with stenting to prevent further propagation of the dissection and ischemic complications. Because of the direction of blood flow, retrograde dissections can often be treated conservatively (ie, without further intervention) (option E).
- 35-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 35*) The syndrome of coronary spasm includes symptoms typical of angina pectoris, but occurring at rest (option A) and typically associated with transient elevation of the ST segments. The clinical findings (symptoms and ECG changes) associated with coronary spasm may occur without ST-segment elevation, and in fact they are often associated with ST-segment depression and/or T-wave changes (option B) and may also at times result from small-vessel or regional coronary dysfunction. Minor elevations of serum C-reactive protein (option C) suggest chronic low-grade inflammation may be involved in the pathogenesis of coronary spasm.¹⁰ Finally, coronary spasm is more common in younger patients and women (option D) than angina pectoris occurring because of obstructive atherosclerosis. So all of the above are correct (option E).

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CHAPTER 36

Definitions of Acute Coronary Syndromes

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

36-1. Coronary artery disease (CAD) accounts for what proportion of all global deaths?

- A. 20%
- B. 30%
- C. 40%
- D. 50%
- E. 60%

36-2. In 2011, the costs associated with myocardial infarction (MI) and coronary heart disease (CHD) in the United States were \$11 billion and \$10 billion, respectively. These costs are projected to do what by 2030?

- A. Decrease by 100%
- B. Decrease by 50%
- C. Stay approximately the same
- D. Increase by 50%
- E. Increase by 100%

36-3. Which of the following concerning acute coronary syndrome (ACS) is *false*?

- A. ACS is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis
- B. ACS encompasses unstable angina (UA), ST-segment elevation MI (STEMI), and acute non–ST-segment elevation MI (NSTEMI)
- C. ACS without myocardial necrosis is defined as UA
- D. Myocardial necrosis is a necessary, but not sufficient, component of either STEMI or NSTEMI
- E. Classification of ACS as STEMI, NSTEMI, or UA is determined within the initial hours of presentation

36-4. Initial triage of patients suspected of having acute coronary ischemia should include consideration which of the following possible alternative conditions?

- A. Myocarditis/myopericarditis
- B. Pulmonary embolism
- C. Gastroesophageal reflux
- D. Sepsis
- E. Any of the above

36-5. Which of the following concerning UA is *false*?

- A. UA is usually secondary to abrupt reduction in myocardial perfusion as a result of nonocclusive coronary thrombosis
- B. UA and NSTEMI have distinct clinical presentations and pathogenesis
- C. The incidence of UA has decreased over the last several decades
- D. The diagnosis of UA relies primarily on clinical history
- E. Patients with UA may present with either rest or minimal exertion angina lasting at least 20 minutes, new-onset severe angina, or crescendo angina

36-6. The risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days in individuals with the highest Thrombolysis in Myocardial Infarction (TIMI) risk scores is:

- A. 25%

- B. 40%
- C. 55%
- D. 70%
- E. 85%

36-7. Historically, myoglobin, creatine kinase, and the cardiac-specific CK-MB isoform have served as serum biomarkers indicating myocardial injury or necrosis. What is the most significant limitation of these biomarkers for the diagnostic evaluation of patients with presumed cardiac chest pain?

- A. Cost of the test
- B. Delay in release into the peripheral blood after onset of injury
- C. Lack of cardiac specificity
- D. Difficulty of use
- E. Instability in vitro

36-8. Which of the following concerning biomarkers of cardiac injury is *false*?

- A. Both troponin I and troponin T are only found in cardiac tissue
- B. Troponin elevation occurs only in the context of ACS
- C. Cardiac troponins demonstrate a graded, dose-dependent association with increasing cardiovascular risk
- D. Changes in cardiac troponins confer an independent and stronger impact on subsequent risk than clinical symptoms or ECG signs
- E. American College of Cardiology/American Heart Association guidelines recommend against the routine measurement of CK-MB for the diagnosis of MI

36-9. Which of the following is *not* one of the criteria that must be present in the proper clinical setting leading to evidence of myocardial necrosis, according to the World Heart Federation's Universal Definition of Myocardial Infarction?

- A. Detection of the rise or fall of troponin or CK-MB with at least one value above the 99th percentile of the upper reference limit (URL), in addition to evidence of myocardial ischemia by one of the following: (1) Symptoms of ischemia; (2) ECG changes indicative of new ischemia (new ST/T-wave changes or new left bundle branch block [LBBB]); (3) Development of new pathologic Q waves on ECG; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- B. Sudden or unexpected cardiac death, involving cardiac arrest, often preceded by symptoms of coronary ischemia and accompanied by new ST-segment elevation or new LBBB, with or without evidence of fresh intracoronary thrombus or an expected rise in serum biomarkers
- C. For patients with normal baseline biomarker levels undergoing PCI, a periprocedural increase of cardiac biomarkers above the 99th percentile URL is deemed abnormal. An increase of a biomarker greater than five times the 99th percentile URL is defined as a PCI-related MI
- D. For patients undergoing coronary artery bypass graft (CABG) with normal baseline biomarker levels, increases greater than five times the 99th percentile URL accompanied by either new pathologic Q waves or new LBBB, angiographically documented graft or native artery occlusion, or new imaging evidence of loss of viable myocardium are labeled as CABG-related MIs
- E. Pathologic evidence of MI

36-10. The global task force that introduced the Universal Definition of Myocardial Infarction also added a clinical classification of MI encompassing most of the common etiologies leading to myocardial necrosis. A patient with a history of recent MI who presents with ST-segment elevation and positive troponin is found to have an occlusive stent thrombosis upon emergent angiography. This would be classified as what type of MI?

- A. Type 1
- B. Type 2
- C. Type 4a
- D. Type 4b
- E. Type 5

ANSWERS

36-1. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 36*) Coronary artery disease accounts for 30% of all global deaths, representing the single most common cause of adult mortality and equivalent to the combined number of deaths caused by nutritional deficiencies, infectious diseases, and maternal/perinatal complications.^{1,2} Recent growth in the global burden of cardiovascular disease (CVD) is primarily attributable to the rising incidence across low- and middle-income countries.³ Among European member states of the World Health Organization (WHO), for example, CVD death

rates for men and women were highest in the Russian Federation and Uzbekistan, respectively, whereas risk was lowest in France and Israel.⁴ Conversely, in the United States, over 15 million Americans, or 6.2% of the adult population, have CHD, with an MI occurring once every 43 seconds.⁵

- 36-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 36*) Health care resource utilization for CHD is significant; over 1.1 million hospital discharges in 2010 listed MI or UA as a primary or secondary diagnosis.⁵ Health care expenditures are also substantial; costs for MI and CHD were approximately \$11 billion and \$10 billion, respectively, in 2011.⁶ These diagnoses constitute two of the most expensive discharge diagnoses and are expected to increase by 100% by 2030. Despite these sobering statistics, important strides in the diagnosis, prevention, and management of CHD have occurred over the past 50 years. In the United States, for example, several population-based studies have shown a reduction in both the incidence and the case fatality rate associated with MI.^{7,8} These favorable trends have been attributed to greater utilization of evidence-based therapies and improvements in the control and burden of risk factors.⁹ Concordant changes in the epidemiology of ACS have occurred over the past 10 years as a result of changing demographics and updated definitions of MI.
- 36-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 36*) The term *acute coronary syndrome (ACS)* is a unifying construct representing a pathophysiologic and clinical spectrum culminating in acute myocardial ischemia. This is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis and is associated with an increased risk of myonecrosis and cardiac death (option A).¹⁰ ACS encompasses UA and ST-segment elevation MI (STEMI) or acute non-ST-segment elevation MI (NSTEMI) (option B). Distinguishing these presentations is predicated on the presence or absence of myocyte necrosis coupled with the electrocardiographic tracing at the time of symptoms. ACS without myocardial necrosis is defined as UA (option C), whereas myocardial necrosis is a necessary, but not sufficient, component of either STEMI or NSTEMI (option D). The diagnosis of ACS relies on integrating clinical information from the patient history with the initial ECG and laboratory results. In the initial hours after presentation, distinguishing between STEMI, NSTEMI, and UA may be difficult because biomarkers of myonecrosis can initially be normal (option E). However, as a result of the life-threatening nature of ACS, it is prudent to have a low threshold in suspecting this diagnosis, and therefore, diagnostic sensitivity is usually favored over specificity.
- 36-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 36*) Initial triage of patients suspected of having acute coronary ischemia should identify patients as having (1) ACS; (2) a non-ACS cardiovascular condition such as myocarditis/myopericarditis (option A), stress-related cardiomyopathy, aortic dissection, or pulmonary embolism (option B); (3) a noncardiac cause of chest pain such as gastroesophageal reflux (option C); or (4) a noncardiac condition that is yet undefined, such as sepsis (option D).¹¹ ACS patients with new ST-segment elevation on the presenting electrocardiogram (ECG) are labeled as having STEMI and should be considered for immediate reperfusion therapy by thrombolytics or percutaneous coronary intervention; those without ST-segment elevation but with evidence of myonecrosis are deemed to have an NSTEMI; and those without any evidence of myonecrosis are diagnosed with UA.
- 36-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 36*) UA is usually secondary to abrupt reduction in myocardial perfusion as a result of nonocclusive coronary thrombosis (option A). In this event, however, the nonocclusive thrombus that developed on a disrupted atherosclerotic plaque does not result in biochemical evidence of myocardial necrosis. Accordingly, UA and NSTEMI can be viewed as very closely related clinical conditions with similar presentations and pathogenesis but variable clinical severity (option B). Nevertheless, given the increased reliance on highly sensitive biomarkers of myocyte necrosis, the incidence of troponin-negative ACS or UA is decreasing (option C).¹² This shift in ACS epidemiology was illustrated in a report from the US Nationwide Inpatient Sample, which demonstrated an 87% decline in the prevalence of UA between 1998 and 2001 but an increase in NSTEMI.¹³ As a result of the lack of objective criteria used to define this condition, UA must be diagnosed from the clinical history (option D) and is thus the most subjective of the ACS diagnoses. There are three principal clinical presentations of UA (option E): (1) rest angina or angina with minimal exertion usually lasting at least 20 minutes; (2) new-onset severe angina (Canadian Cardiovascular Society grade III or higher); and (3) crescendo angina, defined as previously diagnosed angina that has become distinctly more frequent, precipitated by less severe degrees of exertion, or more severe.^{14,15} Despite a clear and consistent definition for UA, the subjective nature of these criteria may compromise diagnostic accuracy, thereby leading to misclassification. In one report, for example, 20% of patients diagnosed with UA and referred for coronary angiography did not have any angiographically apparent obstructive epicardial CAD.¹⁶
- 36-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 36*) Once CAD has been established as the likely cause of chest pain, it is necessary to estimate, or stratify, risk for adverse events using qualitative or quantitative methods. The tempo and severity of chest pain, the extent of electrical abnormality, and the magnitude of serum biomarker elevation all portend a higher risk for adverse events. Among these, biomarker evidence of myocyte necrosis is the strongest and most consistent correlate of risk. Quantitative risk scores provide an alternative and more precise approach to risk stratification. Perhaps the most widely used is the integer-based TIMI risk score, which allots a single point for each of the following in patients with chest pain: age > 65 years; aspirin use within 7 days prior to presentation; ST deviation > 0.5 mm; severe angina; at least three risk factors for CAD; raised cardiac biomarker; and known coronary stenosis.¹⁷ The short-term risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days varied from 1.4% for patients with very low scores (0–1) to 40% for those with the

highest scores (option B).

- 36-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 36*) Serum biomarkers indicating myocardial injury or necrosis are critical elements in the diagnostic evaluation of a patient with presumed cardiac chest pain and are essential to distinguishing between UA and overt infarction. Ideally, such biomarkers would be specific to cardiac muscle, would be absent from nonmyocardial tissue, would be released quickly into the peripheral blood after onset of injury, and would reflect the magnitude of necrosis. Moreover, the marker should be easy to use, quick and inexpensive to measure, and stable in vitro. Historically, myoglobin, creatine kinase, and the cardiac-specific CK-MB isoform have served this purpose in the diagnosis of MI. The main limitation of these markers is the lack of cardiac specificity (option C) because each may also be variably released from skeletal muscle and other tissues, such as the tongue, small intestine, uterus, and prostate. As a result, earlier definitions of MI did not require the presence of these cardiac biomarkers for diagnosis but rather considered their elevation along with clinical symptoms and electrical signs of myocardial ischemia.¹⁸
- 36-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 36*) Troponin I (TnI) and troponin T (TnT) are found only in myocardial tissue (option A), therefore elevated levels of either marker reflect myocyte injury. The advantages to cardiac troponin (cTn) testing (TnI or TnT) notwithstanding, as with any diagnostic test, gains in sensitivity occur at the expense of specificity. Several studies have shown that troponin elevations may occur in non-acute coronary syndrome clinical settings (option B), such as heart failure, renal dysfunction, and pulmonary embolism. Troponin may even be detected in apparently healthy community-dwelling adults, as shown in the Dallas Heart Study.¹⁹ In that report, investigators found the following clinical conditions independently associated with detectable levels of cardiac troponin: left ventricular hypertrophy, diabetes mellitus, chronic kidney disease, and heart failure. As a result, the diagnosis of type 1 MI requires not only the presence of elevated cardiac troponin, but also a clinical context supporting an ischemic etiology. From a prognostic perspective, cTns demonstrate a graded, dose-dependent association with increasing cardiovascular risk (option C). Antman et al²⁰ illustrated this relationship in a post hoc analysis of a randomized trial evaluating various pharmacologic approaches in patients with ACS, demonstrating that unadjusted mortality rates at 42 days increased from 1.0% to 7.5% among those with the lowest versus highest levels of cTn. In addition, changes in cTn confer an independent and stronger impact on subsequent risk than clinical symptoms, ECG signs, or other biomarkers (option D).²¹ Given these benefits of assessing and formulating clinical decisions based on detecting cTn, the Universal Definition of MI considers this biomarker preferentially over CK-MB. In addition, American College of Cardiology/American Heart Association guidelines no longer consider the routine measurement of CK-MB as necessary for the diagnosis of MI, and they provide a class III recommendation against routine use of this test (option E).¹¹
- 36-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 36*) In 2007, the World Heart Federation, in concert with major European and American cardiovascular societies, convened a global task force to introduce the Universal Definition of MI. The result was a clinicopathologic classification of MI that considers five different MI types, each representing a distinct clinical and pathologic entity culminating in myocyte necrosis. The Universal Definition has been updated twice, with the most recent iteration published in 2012.²² The new accepted universal criteria for diagnosing an acute MI state that one of five criteria must be present in the proper clinical setting leading to evidence of myocardial necrosis. Options A, B, D, and E are four of these criteria. Option C is incorrect; for a diagnosis of MI to be made in the event of sudden or unexpected cardiac death, involving cardiac arrest, often preceded by symptoms of coronary ischemia and accompanied by new ST-segment elevation or new LBBB, evidence of fresh intracoronary thrombus must be detected by angiography or autopsy when death occurred before blood was obtained or an expected rise in serum biomarkers could occur.
- 36-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 36*) In addition to revising the criteria for MI diagnosis, the global task force added a clinical classification of MI encompassing most of the common etiologies leading to myocardial necrosis. Each etiology of MI differs with respect to short- and long-term mortality rates. Type 1 MI (option A) occurs as a result of a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection. Type 2 MI (option B) occurs secondary to ischemia from either increased oxygen demand or decreased supply, for example, coronary artery spasm, embolism, anemia, arrhythmias, hypertension, or hypotension. Type 3 MI occurs in the setting of sudden cardiac death, including cardiac arrest, that may be preceded by ischemic symptoms, accompanied by new ST-segment elevation, new LBBB, or evidence of fresh thrombus by coronary arteriography or autopsy. Death could occur before blood samples are obtained or before cardiac biomarkers appear in the blood. Type 4 MI is associated with PCI and is further classified as Type 4a or 4b. Type 4a MI (option C) is associated with PCI. Type 4b MI (option D) is associated with stent thrombosis as documented by angiography or at autopsy. Type 5 MI (option E) is associated with CABG.

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CHAPTER 37

Pathology of Myocardial Infarction and Sudden Death

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

37-1. Which of the following statements about myocardial energy metabolism is *correct*?

- A. Under normal aerobic conditions, most cardiac energy is derived from glycolysis
- B. Decreased adenosine triphosphate (ATP) production due to ischemia results in decreased cytosolic Na^+ and cell swelling
- C. Myocardial ischemia primarily affects mitochondrial metabolism and oxidative phosphorylation
- D. Reversibly injured myocytes are characterized by cell membrane breaks and amorphous densities in the mitochondria
- E. Only one-third of the ATP used by the heart goes to contractile shortening

37-2. A 63-year-old man presents to the emergency department with onset of chest pain while washing his car. He has a history of angina and MI due to culprit LAD disease. Which of the following could be a contributor to smaller infarct size?

- A. The absence of coronary collateral vessels
- B. The extended duration of coronary occlusion
- C. The earlier occlusion of the same coronary artery
- D. Ventricular remodeling
- E. None of the above

37-3. A 67-year-old man has an acute myocardial infarction (MI) with occlusion of the LAD. He receives thrombolysis and coronary artery revascularization by PCI, but in the following months, he develops left ventricular systolic dysfunction. Which of the following is *not correct* about the mechanisms of reperfusion injury?

- A. Reperfusion-mediated infiltration of neutrophils into the ischemic region causes inflammation
- B. Reperfusion results in decreased intracellular Ca^{2+} , ATP depletion, and cell death
- C. Rapid restoration of physiologic pH contributes to reperfusion injury
- D. Reperfusion generates oxidative stress that extends the myocardial injury
- E. Decreased nitric oxide allows for neutrophil accumulation and reduced coronary blood flow during reperfusion

37-4. Which of the following is *not* a feature of myocardial hibernation?

- A. Decreased calcium responsiveness
- B. Upregulation of nitric oxide synthase, COX-2, and heat shock protein
- C. Decreased number of sarcomeres
- D. Upregulation of myosin, titin, and actinin
- E. Chronic ischemia with contractile dysfunction

37-5. A 45-year-old woman is recovering in the hospital from a myocardial infarct with ST-segment elevation. Which of the following is *correct* about plaque morphology?

- A. The majority of thrombi leading to acute MI are caused by plaque erosion
- B. Plaque erosions are more common in men than in women
- C. Most plaques occur in the proximal portion of the coronary arteries
- D. Most thrombi in plaque rupture are organizing (> 1 day)
- E. All of the above are correct

37-6. Which of the following depicts the *correct* pathologic progression of nonreperfused myocardial infarcts?

- A. Wavy fibers, neutrophil infiltration, coagulation necrosis, fibroblast activity
- B. Fibroblast activity, granulation tissue, neutrophil infiltration, coagulation necrosis
- C. Wavy fibers, coagulation necrosis, hypereosinophilic myocyte, neutrophil infiltration

- D. Fibroblast activity, wavy fibers, neutrophil infiltration, coagulation necrosis
- E. None of the above

- 37-7.** A 59-year-old man presents with chest pain that precipitated while he was mowing the lawn. He did not seek medical attention until 4 hours after the onset of symptoms. Which of the following is *correct* about reperfusion following acute MI?
- A. Myocardium is not salvageable 4 hours after the onset of chest pain
 - B. In perfused infarcts, neutrophils are concentrated at the margins
 - C. The rate of healing by fibroblasts is greater in nonreperfused infarcts
 - D. Reperfused infarcts have areas of necrosis at the center mixed with noninfarcted myocardium
 - E. Reperfusion within 6 hours of the onset of chest pain is likely to result in significant myocardial salvage
- 37-8.** Which of the following is *incorrect* about myocardial remodeling following MI?
- A. Myocardial infarction induces a systemic inflammatory response
 - B. Transition to M2 macrophages causes expansion of the infarcted area
 - C. M1 macrophages set up the proinflammatory environment following an infarct
 - D. Prolonged M1 macrophage activation results in expansion of the injured ventricular wall
 - E. All of the above are incorrect
- 37-9.** A 64-year-old woman developed an aneurysm following an MI caused by occlusion of the LAD. Which of the following is *correct* about aneurysms?
- A. Patients receiving reperfusion therapy have a higher incidence of aneurysms
 - B. Female gender is an independent determinant of aneurysm formation after infarction
 - C. The wall of a true aneurysm consists of fibrous pericardium
 - D. Subendocardial infarcts are the most likely to result in true aneurysms
 - E. All of the above are correct
- 37-10.** Which of the following is *not correct* regarding complications of MI?
- A. Right ventricular wall rupture is much more common than left ventricle rupture
 - B. Anticoagulation should be discontinued or used with caution in the presence of significant (≥ 1 cm) pericardial effusion after MI
 - C. Cardiogenic shock is caused by decreased systemic cardiac output with adequate intravascular volume
 - D. Ventricular arrhythmias are associated with decreased survival post-MI
 - E. Right ventricular cardiogenic shock is associated with younger age

ANSWERS

- 37-1. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 37*) The normal function of the heart muscle is supported by high rates of myocardial blood flow, oxygen consumption, and combustion of fat and carbohydrates (glucose and lactate). Under normal aerobic conditions, cardiac energy is derived from fatty acids, supplying 60% to 90% of the energy for ATP synthesis (option A). The rest (10% to 40%) comes from the oxidation of pyruvate formed from glycolysis and lactate oxidation. Almost all of the ATP formed comes from oxidative phosphorylation in the mitochondria; only a small amount of ATP ($< 2\%$) is produced by glycolysis. Approximately two-thirds of the ATP used by the heart goes to contractile shortening (option E), and the remaining third is used by sarcoplasmic reticulum Ca^{2+} ATPase and other ion pumps. Myocardial ischemia primarily affects mitochondrial metabolism, resulting in a decrease in ATP formation by shutting off oxidative phosphorylation (option C). Decreased ATP inhibits Na^+/K^+ -ATPase, increasing intracellular Na^+ and Cl^- , leading to cell swelling (option B). Reversibly injured myocytes are edematous and swollen from the osmotic overload. Irreversibly injured myocytes contain shrunken nuclei with marked chromatin margination. The two hallmarks of irreversible injury are cell membrane breaks and the mitochondrial presence of small osmiophilic amorphous densities (option D).
- 37-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 37*) Myocardial ischemia occurs when oxygen and nutrient supply do not meet myocardial demand, and necrosis or infarction occurs when ischemia is severe and prolonged. The extent of coronary collateral flow is one of the principal determinants of infarct size. Indeed, at autopsy, it is common to see chronic total coronary occlusion and an absence of MI in the distribution of that artery. The absence of myocardial ischemia following coronary artery occlusion is associated with the presence of well-developed collateral vessels (option A). Reimer and Jennings showed that if a canine coronary artery was occluded for 15 minutes, for 40 minutes, for 3 hours, or permanently for 4 days, myocardial necrosis progressed as a “wave front phenomenon.”^{1,2} The extent of myocardial necrosis therefore depended on the duration of coronary occlusion (option B). Other than the presence of collateral circulation, factors that influence infarct size include preconditioning (option C), which may greatly reduce

infarct size, and reperfusion. Transmural infarcts may increase in size for weeks after the initial event, and the degree of this expansion is associated with a decrease in the survival rate. The processes involved in postinfarction ventricular dilatation are known as ventricular remodeling. In general, the transmural extent of necrosis is a major determinant of infarct expansion (remodeling) based on large infarct size and the persistence of the occlusion (option D).

- 37-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 37*) The process of restoring blood flow to ischemic myocardium has shown utility in limiting cell death in the presence of severe ischemia. Reperfusion, however, has paradoxical effects on myocardium that can result in adverse reactions, termed reperfusion injury. During reperfusion, the myocardium is subject to abrupt biochemical and metabolic changes governed by several mediators that interact with each other in complex ways. Reperfusion markedly enhances the infiltration of neutrophils into the ischemic region and amplifies the inflammatory response (option A). At the time of myocardial reperfusion, there is an abrupt increase in intracellular Ca^{2+} known as the calcium paradox (option B). This intracellular Ca^{2+} causes opening of the mitochondrial permeability transition pore (PTP), which uncouples oxidative phosphorylation, resulting in ATP depletion and cell death. In addition, studies have shown that reperfusion of ischemic myocardium generates reactive oxygen species (oxygen paradox). This oxidative stress results in the extension of the myocardial injury beyond that induced by ischemia alone (option D). A key mechanism involves the reduction of the bioavailability of the nitric oxide, which normally inhibits neutrophil accumulation, inactivates superoxide radicals, and improves coronary blood flow (option E). Further contributing to reperfusion injury is the rapid restoration of physiologic pH (option C) that occurs after washout of lactic acid and the activation of the sodium-hydrogen exchanger and the sodium-bicarbonate symporter. The final consequence of reperfusion injury is left ventricular (LV) systolic dysfunction leading to increased morbidity and mortality.
- 37-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 37*) In the early 1980s, Rahimtoola et al.³ found significant improvement in left ventricular function after coronary revascularization in a subset of patients with depressed ventricular performance. They postulated that the mechanism of poor myocardial contractility was chronic ischemia (option E), which could be improved by revascularization. The premise behind this rationale was dependent on the surviving myocardium being in a functional, albeit depressed, state, suggesting that the myocardium may adapt to chronic ischemia by decreasing its contractility but preserving viability. Chronically hibernating myocardium demonstrates changes in adrenergic control and calcium responsiveness (option A). Substances that are upregulated in chronic hibernating myocardium include heat shock protein, hypoxia-inducible factor, inducible nitric oxide synthase, cyclooxygenase-2, and monocyte chemotactic protein (option B). Morphologically, hibernating myocytes show a loss of contractile elements, the sarcomeres (option C), with increased glycogen. There is a disorderly increase in cytoskeletal desmin, tubulin, and vinculin, with a decrease in contractile proteins myosin, titin, and actinin (option D).
- 37-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 37*) The vast majority of MIs occur in patients with coronary atherosclerosis, with > 90% associated with superimposed luminal thrombi. Arbustini et al.⁴ found coronary thrombi in 98% of patients dying with clinically documented acute MI, and of those thrombi, 75% were caused by plaque rupture and 25% by plaque erosion (option A). There are gender differences in the causation of coronary thrombi leading to acute MI: Arbustini et al.⁴ showed that 37% of thrombi in women were erosion compared with only 18% in men (option B). The thrombus age also varies; the majority of acute thrombi (< 1 day) have been observed in plaque rupture, whereas the majority of thrombi in plaque erosion are organizing (> 1 day)⁵ (option D). The majority of thin cap fibroatheromas, acute and healed ruptures, and lesions with fibroatheromas occur predominantly in the proximal portion of the three major coronary arteries (option C), and about 50% arise in the midportion of these arteries.
- 37-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 37*) The earliest morphologic characteristic of MI that can be discerned and observed between 12 and 24 hours after the onset of chest pain is the hypereosinophilic myocyte. It has been suggested in experimentally induced infarction that the appearance of "wavy fibers" (1) may be the earliest change and is thought to be the result of stretching of the ischemic noncontractile fibers by the adjoining viable contracting myocytes. Neutrophil infiltration (2) is present by 24 hours at the border areas. As the infarct progresses between 24 and 48 hours, coagulation necrosis (3) is established with various degrees of nuclear pyknosis, early karyorrhexis, and karyolysis. At 3 to 5 days, the central portion of the infarct shows loss of myocyte nuclei and striations. The influx of inflammatory cells, including mast cells, induces a cascade of chemokines, which suppress further inflammation and result in scar tissue.⁶ Macrophages and fibroblasts (4) begin to appear in the border areas. By 1 week, neutrophils decline, and granulation tissue is established with neocapillary invasion and lymphocytic and plasma cell infiltration. By the second week, fibroblasts are prominent, and there is continued removal of the necrotic myocytes as the fibroblasts are actively producing collagen and angiogenesis occurs in the area of healing. Option A is therefore correct.
- 37-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 37*) If reperfusion occurs within 4 to 6 hours after the onset of chest pain or electrocardiographic (ECG) changes, there is myocardial salvage (option A), and the infarct is likely to be subendocardial without transmural extension (option E). Within a few hours of reperfusion, neutrophils are evident within the area of necrosis, but they are usually sparse. In contrast to nonreperfused infarcts, neutrophils do not show concentration at the margins (option B). However, reperfused infarcts often demonstrate areas of necrosis at the periphery with interdigitation with noninfarcted myocardium (option D). Macrophages begin to appear by day 2 or 3, and stromal cells show enlarged nuclei and nucleoli by days 3 and 4. Neutrophil debris, which may be concentrated at the border areas in cases of incomplete reperfusion, is seen by 3 to 5 days. Fibroblasts appear by days 3 to 5, with an accelerated rate of healing compared with nonreperfused infarcts (option C).

- 37-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 37*) Myocardial remodeling is defined as changes in size, shape, and function of the heart occurring secondary to molecular, cellular, and interstitial events after MI. Left ventricular remodeling begins within the first few hours after an infarct and continues to progress, and the infarcted myocardium undergoes rapid turnover during the first 1 to 2 weeks after MI. MI generates a systemic inflammatory response (option A), with activation of the complement cascade, transforming growth factor- β , and chemokines and free radical generation. During the healing phase, infiltrating monocytes differentiate into macrophages, which, along with mast cells, accumulate in the healing scar, inducing fibroblast proliferation. Classically activated M1 macrophages are the first line of defense that influences the subsequent phase of the healing process by M2 macrophages. The prolonged presence of M1 macrophages extends the proinflammatory environment (option C) and causes expansion of the infarcted area (option B). A delayed transition to M2 macrophages thus hampers the formation of scar tissue, predisposing to heart failure development as a result of expansion of the injured ventricular wall (negative remodeling) (option D). Improved healing may be attained by modulating macrophage polarization toward the M2 phenotype, thus promoting the resolution of inflammation and improved infarct healing.
- 37-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 37*) Single-vessel disease, absence of previous angina, total LAD occlusion, and female gender (option B) are independent predictors of left ventricular aneurysm formation after anterior infarction. Patients receiving reperfusion therapy and exhibiting a patent infarct-related artery have a lower incidence of aneurysm formation (option A). A large acute transmural myocardial infarction that has undergone expansion is the most likely infarct to result in a true aneurysm (option D). Morphologically, the wall of a true aneurysm develops after MI, and it consists of fibrous tissue (option C) with or without interspersed myocytes. In contrast, the wall of a false aneurysm is formed by fibrous pericardium (not from the left ventricular MI and healing).
- 37-10. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 37*) The complications of MI may manifest immediately or they may appear late, and they depend on the location and extent of infarction. The acute complications consist of arrhythmias and sudden death, cardiogenic shock, infarct extension, fibrinous pericarditis, cardiac rupture, and mural thrombus and embolization. Ventricular arrhythmias are important markers of electrical instability and are associated with decreased survival in the acute post-MI phase. Left ventricular wall rupture is much more common than right ventricle rupture (option A). Although reperfusion therapy has reduced the incidence of cardiac rupture, late thrombolytic therapy may increase the risk of cardiac rupture. Heart failure after MI ranges from pulmonary congestion to profound organ hypoperfusion or cardiogenic shock. Cardiogenic shock is caused by decreased systemic cardiac output in the presence of adequate intravascular volume (option C). Right ventricular cardiogenic shock after acute infarction is associated with younger age, a lower prevalence of previous infarctions, fewer anterior infarct locations, and less multivessel disease (option E). Pericardial effusion after MI usually takes several months to reabsorb. Anticoagulation should be discontinued in the presence of a significant (≥ 1 cm) or enlarging pericardial effusion (option B).

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CHAPTER 38

Molecular and Cellular Mechanisms of Myocardial Ischemia/Reperfusion Injury

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

38-1. Which of the following is *not* a determinant of infarct size?

- A. Time to reperfusion
- B. The presence of collaterals
- C. Blood pressure
- D. Temperature
- E. Ischemia/reperfusion injury

38-2. Which of the following does *not* contribute to myocyte necrosis after reperfusion?

- A. Sarcolemma disruption and calcium overload
- B. ATP depletion and reversal of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, resulting in increased intracellular calcium
- C. The no-reflow phenomenon
- D. Tissue edema
- E. Autophagy

38-3. Which of the following is *true* about intracellular Ca^{2+} during ischemia-reperfusion injury?

- A. The $\text{Na}^+/\text{Ca}^{2+}$ exchanger extrudes Ca^{2+} from the cytoplasm
- B. Calpains are activated by increases in Ca^{2+}
- C. The RyR2 does not contribute to increased intracellular Ca^{2+}
- D. Sarcolemma membranes remain intact
- E. Calpains are only active at low pH

38-4. Which of the following is *correct* regarding mitochondrial function during reperfusion?

- A. Mitochondrial calcium decreases
- B. The mitochondrial permeability transition pore (MPTP) is open during acidosis
- C. Cyclophilin D closes the MPTP
- D. Restoration of DNA synthesis occurs immediately following reperfusion
- E. Succinate levels increase during ischemia and scavenge reactive oxygen species (ROS) following reperfusion

38-5. Which of the following is *not true* regarding coronary circulation during reperfusion injury?

- A. Interstitial edema occurs in part because of a dysfunctional endothelial barrier
- B. Edema peaks at 120 minutes and again at 7 days
- C. The release of vasodilators from the culprit lesion dilates the microvasculature
- D. Cellular aggregates from the culprit lesion impair flow in the microcirculation
- E. Hemorrhage of the microcirculation is associated with an adverse prognosis

38-6. Which of the following is *true* of ischemic preconditioning (IPC)?

- A. Repeated episodes of ischemia increase reperfusion injury
- B. Ischemic preconditioning results in a cardioprotective phase 7 days after preconditioning
- C. Ischemic preconditioning results in the release of protective autacoids
- D. Ischemic preconditioning is thought to increase calcium load

E. The presence of angina before an MI is associated with larger injuries following MI

38-7. Which of the following is *true* about ischemic postconditioning?

- A. In preclinical models, intermittent reperfusion reduces infarct size
- B. Ischemic postconditioning is unlikely to involve the same mechanisms as preconditioning
- C. Early clinical studies demonstrate a benefit of ischemic postconditioning on improving outcomes following myocardial infarction in humans
- D. Ischemic postconditioning increases myocardial edema
- E. Ischemic postconditioning increases infiltration by polymorphonuclear monocytes

38-8. Which of the following is *not correct* regarding remote ischemic conditioning (RIC)?

- A. RIC is likely mediated by bloodborne factors
- B. RIC requires an intact neural pathway to be effective
- C. The mechanism of RIC is likely to involve the RISK and SAFE pathways
- D. RIC results in the release of autacoids
- E. Treatment with SDF-1 can increase infarct size by mimicking RIC

38-9. Which of the following pharmacologic options may reduce ischemia-reperfusion injury?

- A. Cyclosporine A
- B. Adenosine
- C. Hypothermia
- D. Metoprolol
- E. Antioxidants

38-10. When does myocardial edema peak after reperfusion following acute myocardial infarction?

- A. Immediately after reperfusion
- B. 7 days post reperfusion
- C. 3 days post reperfusion
- D. A and B
- E. B and C

ANSWERS

38-1. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 38*) Shorter time to reperfusion and an increased number of collaterals are associated with smaller infarct sizes (options A and B). Lower temperatures and larger ischemia/reperfusion injury are associated with larger infarct sizes (options D and E). Blood pressure by itself is not directly associated with infarct size (option C).

38-2. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 38*) Calcium overload that results from disruption of the sarcolemma and reversal of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger contribute to reperfusion injury (options A and B).¹ Impairment of the microcirculation via the no-reflow phenomenon or by compression through tissue edema can exacerbate reperfusion injury (options C and D).^{2,3} Autophagy is not known to contribute to reperfusion injury (option E).

38-3. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 38*) Altered Ca^{2+} handling is one of the most prominent and relevant aspects of cardiomyocyte reperfusion. Reperfusion causes further Ca^{2+} influx through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger in response to Na^+ overload (option A). An important consequence of increased Ca^{2+} is activation of the Ca^{2+} -dependent proteases calpains. Calpains translocate to the sarcolemma during ischemia in response to Ca^{2+} overload but are activated only during reperfusion when intracellular pH is normalized because they are inhibited by low pH (options B and E).⁴ When the Ca^{2+} capacity of the sarcoplasmic reticulum (SR) is exceeded, Ca^{2+} is released back into the cytosol through the ryanodine receptor channel (RyR2) (option C). Excessive contractile activation may cause hypercontracture, resulting in disruption of cardiomyocyte architecture that can cause sarcolemma rupture and cell death (option D).

38-4. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 38*) Restoration of the mitochondrial membrane potential favors mitochondrial Ca^{2+} uptake through the Ca^{2+} uniporter and Ca^{2+} overload (option A).⁵ Mitochondrial permeability transition is caused by the opening of the MPTP. During ischemia, the MPTP does not open because of the inhibiting effect of intracellular acidosis (option B). Cyclophilin D modulates the sensitivity of MPTP to Ca^{2+} (option C).⁶ Reperfusion results in immediate restoration of respiration, proton gradient across the inner mitochondrial membrane, and ATP synthesis (option D). Reactive oxygen species levels increase following reperfusion, in part, because of

oxidation of the excess succinate that builds up during ischemia (option E).^{7,8}

- 38-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 38*) Interstitial edema develops as a consequence of increased interstitial osmolarity from increased ion and catabolite concentrations and a dysfunction of the endothelial barrier during myocardial ischemia (option A). Edema development during reperfusion follows a bimodal pattern, where an initial maximum of water content after 120 minutes is associated with the beginning of leukocyte infiltration and a secondary peak after 7 days is associated with enhanced collagen deposition (option B).^{9,10} The release of vasoconstrictor substances such as thromboxane, serotonin, and endothelin from the culprit lesion into the microcirculation, in conjunction with the impairment of endothelial function by ischemia/reperfusion per se or by tumor necrosis factor- α (TNF- α), can contribute to enhanced vasoconstrictor responsiveness of the microcirculation during myocardial ischemia/reperfusion (option C).¹¹⁻¹³ Cellular aggregates are either released from the epicardial atherosclerotic culprit lesion and dislodged into the microcirculation or are formed in the coronary microcirculation, resulting in impaired flow (option D). No-reflow and hemorrhage carry an adverse prognosis (option E).^{14,15}
- 38-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 38*) Repeated episodes of ischemia decrease reperfusion injury (option A).^{16,17} IPC has been shown to induce two distinct windows of cardioprotection. The first, usually referred to as classic preconditioning, occurs immediately after the IPC stimulus and lasts 2 to 3 hours, followed by a disappearance of the effect. This is followed by a second window of protection, or delayed effect, appearing 12 to 24 hours later and lasting 48 to 72 hours (option B).^{18,19} The sublethal cycles of short bursts of ischemia and reperfusion, which make up the IPC stimulus, produce a number of endogenous biological factors (i.e., autacoids) from the myocyte, including adenosine, bradykinin, endothelin, acetylcholine, and opioids, which can bind to their respective receptors on the plasma membrane. This will direct the appropriate cardioprotective communication pathway that will convey the protective signal to the mitochondria (option C). Although the end effectors of cardioprotection in classical and delayed IPC remain unclear, it has been suggested that preservation of mitochondrial function with less calcium overload, attenuated ROS production, and MPTP inhibition all contribute to the protective effect (option D).²⁰⁻²² The presence of angina before an MI is associated with smaller injuries following MI (option E).²³
- 38-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 38*) Ischemic postconditioning (IPost) confers myriad protective effects, including the preservation of endothelial function, reduced levels of myocardial edema, reduced levels of oxidative stress, and reduced neutrophil accumulation (options A, D, and E).²⁴ IPost has been shown to reduce myocardial infarction size in rodents, rabbits, pigs, and other species including humans, although the cardioprotective effects of IPost do not appear to be as robust as with ischemic preconditioning.^{25,26} Mechanistically, IPost appears to share many of the same signaling mechanisms recruited at the time of reperfusion by ischemic preconditioning (option B).^{25,27} While animal data are promising, early phase clinical studies have yielded mixed results (option C).²⁸
- 38-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 38*) Remote ischemic conditioning is the phenomenon whereby the application of one or more brief cycles of nonlethal ischemia and reperfusion to an organ or tissue protect the heart against a lethal episode of acute reperfusion injury. Blood taken from a rabbit that has been preconditioned reduces MI size when transfused into a naïve rabbit, suggesting that RIC occurs via bloodborne factors (option A). The generation of this cardioprotective factor has been shown to be dependent on an intact neural pathway.²⁹ The exact factor remains unknown, but SDF-1 is a candidate (option E).²⁵ RIC involves the release of autacoid and depends on an intact neural system (options B and D). The mechanism of RIC is likely to involve the RISK and SAFE pathways (option C).³⁰
- 38-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 38*) The history of pharmacologic cardioprotection has been hugely disappointing, with adenosine, antioxidants, magnesium, calcium channel blockers, anti-inflammatory agents, erythropoietin, and atorvastatin all failing to reduce myocardial infarction size or to improve clinical outcomes (options A, B, C, and E).^{24,31} Initial clinical trials using early metoprolol in patients with acute myocardial infarction have suggested a reduction in infarct size (option D).³² Large clinical studies are under way.
- 38-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 38*) Edema development during reperfusion follows a bimodal pattern, where an initial maximum of water content after 120 minutes is associated with a beginning leukocyte infiltration, and a secondary peak after 7 days is associated with enhanced collagen deposition (options A, B, and C).^{9,10,32} It has been proposed that edema during reperfusion reflects the area at risk on cardiac magnetic resonance (CMR), but such a bimodal pattern raises questions about the use of T2-weighted edema measurement for AAR delineation.³³

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CHAPTER 39

Evaluation and Management of Non–ST-Segment Elevation Myocardial Infarction

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 39-1.** Which of the following factors is associated with a low likelihood that chest pain is caused by myocardial ischemia attributable to obstructive coronary artery disease (CAD)?
- A. Known coronary disease (particularly recent PCI)
 - B. Typical angina reproducing prior documented angina
 - C. Hemodynamic or ECG changes during pain
 - D. Dynamic ST-segment elevation or depression of ≥ 1 mm
 - E. T waves flat or inverted < 1 mm
- 39-2.** A 55-year-old woman with a history of hypertension and obstructive sleep apnea presents with two days of an intermittent “squeezing” sensation in her chest. The last episode was approximately six hours ago. Which of the following is *true* about the use of the electrocardiogram to diagnosis an acute coronary syndrome?
- A. Persistent 0.5 mm ST segment depression is strongly suggestive of an acute coronary syndrome
 - B. T-wave inversions do not localize well the territory of myocardial ischemia
 - C. The presence of ST depressions confers a higher risk of 30-day mortality
 - D. The presence of isolated T-wave inversions confers a worse prognosis compared with ST depression
 - E. None of the above are true
- 39-3.** A 52-year-old woman presents with an episode of substernal chest pressure. An initial conservative (“ischemia-guided”) strategy is selected, and she undergoes stress testing. Which of the following findings would be consistent with a low-risk result, supporting ongoing medical management without coronary angiography with the intent to perform percutaneous coronary intervention (PCI)?
- A. Duke treadmill score of 6
 - B. Echocardiographic wall motion abnormality (involving > 2 segments) developing at a heart rate of 120 beats per minute
 - C. Lung uptake on thallium scanning
 - D. Large stress-induced perfusion defect
 - E. Exercise-related left ventricular ejection fraction $< 35\%$
- 39-4.** A 76-year-old man, an active smoker, with a history of diabetes and hypertension, presents with accelerating angina over the past week that is now present at rest. In addition to his age and the presence of ≥ 3 risk factors for CAD, all of the following would also put this patient at higher risk, according to the TIMI Risk Score, *except*:
- A. Known coronary artery stenosis $\geq 50\%$
 - B. Aspirin use within the past 7 days
 - C. ≥ 2 episodes of angina within the past 24 hours
 - D. ST changes ≥ 1 mm on ECG
 - E. Positive cardiac biomarkers
- 39-5.** Which of the following is *not true* about ticagrelor?
- A. Ventricular pauses are a known side effect of ticagrelor that usually develop early after treatment initiation, tend to decrease in frequency over time, are rarely symptomatic, and are not usually associated with clinically significant bradycardia
 - B. Dyspnea tends to occur early after starting the drug in 10% to 15% of treated patients, is not associated with evidence of heart failure, and usually lasts less than a week.

- C. Dyspnea and ventricular pauses are thought to be mediated by interference with adenosine reuptake in erythrocytes
- D. Ticagrelor is a twice daily, reversible ADP antagonist, and hence its antiplatelet effects are no longer present within 12 hours of discontinuation
- E. Ticagrelor is preferred over clopidogrel in the management of patients with acute coronary syndromes when possible

39-6. In selecting a parenteral anticoagulant to treat patients with unstable angina/NSTEMI, which of the following is *true* about the evidence base supporting the use of fondaparinux compared with enoxaparin?

- A. In clinical trials, fondaparinux has been shown to reduce the composite risk of death, MI, or refractory ischemia when compared with enoxaparin
- B. No meaningful differences in bleeding risk have been observed with fondaparinux over enoxaparin
- C. The risk of catheter-related thrombotic complications is higher in patients referred for percutaneous coronary artery intervention who were initially treated with enoxaparin versus fondaparinux
- D. A criticism of the OASIS 5 trial that compared fondaparinux with enoxaparin was that patients with renal failure were allowed into the trial, and the hazard was driven by this group
- E. Fondaparinux has received a class I recommendation for use in patients with unstable angina/NSTEMI by the ACCF/AHA

39-7. A 39-year-old woman presents to the emergency room with chest pain and marked ST segment changes. She continues to complain of crushing chest pain that began abruptly 2 hours ago. Her brother has a history of aortic dissection at a young age. She is referred for urgent coronary angiography, which is shown in [Figure 39-1](#). Based on the angiographic findings and the patient's clinical picture, which of the following is the most likely diagnosis?

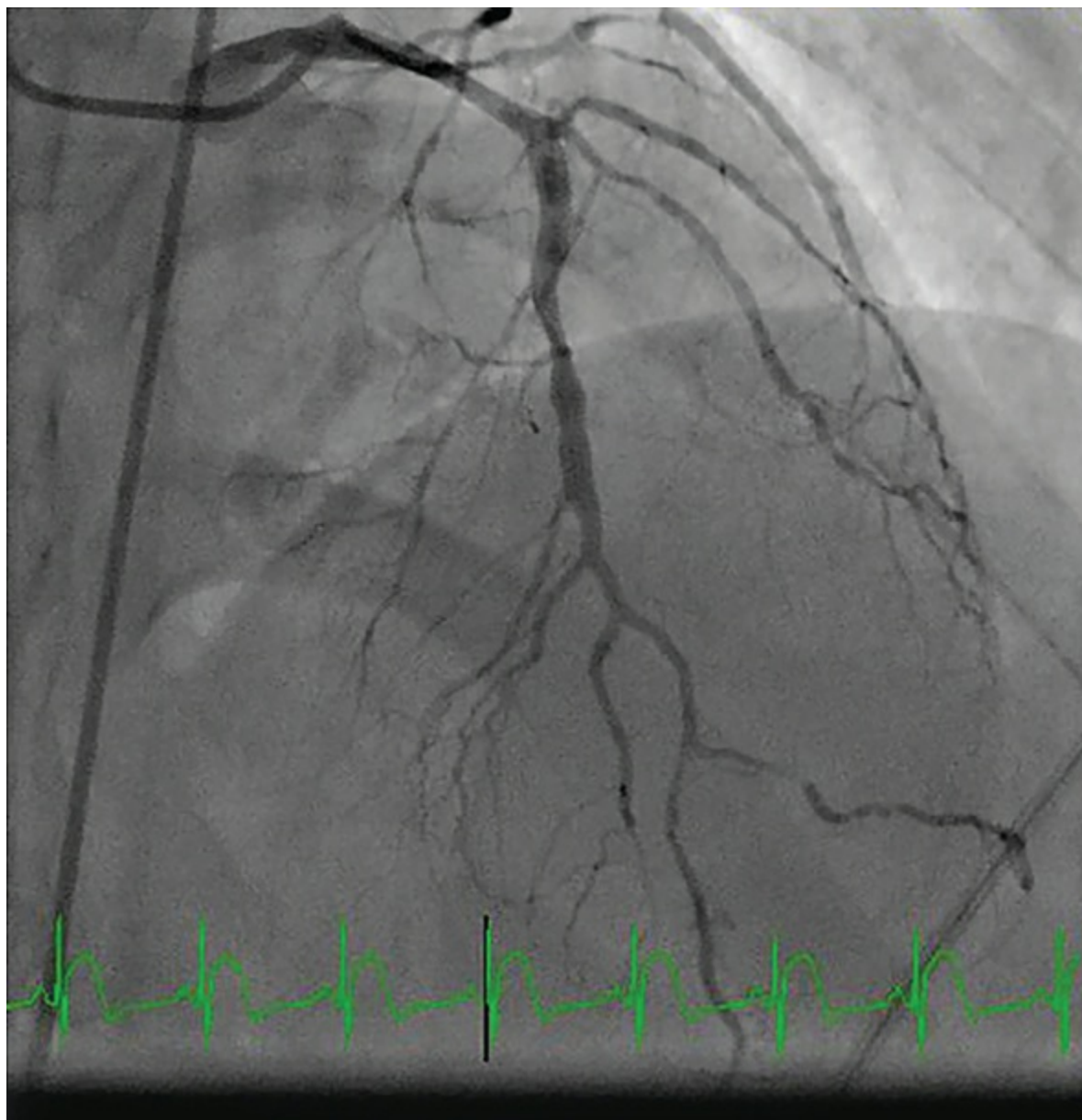


FIGURE 39-1 Coronary angiogram for the patient described in question 39-7.

- A. Acute plaque rupture (type I) myocardial infarction in the setting of atherosclerotic CAD
- B. Coronary artery embolization
- C. Coronary artery dissection
- D. Aortic dissection with extension into the coronary arteries
- E. Takayasu arteritis

39-8. A 52-year-old female cigarette smoker presents with chest pain and ST segment elevations in leads V4 to V6 on a 12-lead ECG, which abruptly resolve accompanied by the resolution of chest pain with a dose of sublingual nitroglycerin in the emergency room. She undergoes coronary angiography, which demonstrates only a 60% stenosis in the circumflex artery. A diagnosis of variant angina is made. All of the following are potentially beneficial treatments *except*:

- A. Nifedipine
- B. Amlodipine

- C. Atorvastatin
- D. Isosorbide mononitrate
- E. Metoprolol

39-9. A 65-year-old woman presents with two days of chest pain and progressive dyspnea. She has anterolateral ST elevations, and her troponin is 5 times the upper limit for normal. She undergoes coronary angiography and ventriculography, which is shown in [Figure 39-2](#). Which of the following statements is *true* about the underlying diagnosis?

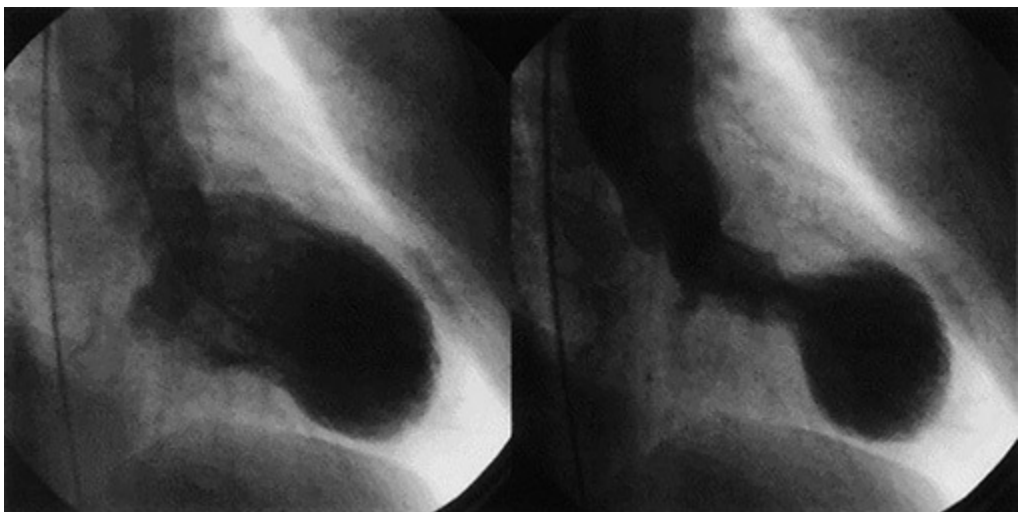


FIGURE 39-2 Left ventriculogram for the patient described in question 39-9. (Reproduced with permission from Abe Y, Kondo M, Matsuoka R, et al. Assessment of clinical features in transient left ventricular apical ballooning, *J Am Coll Cardiol*. 2003 Mar 5;41(5):737-742.)

- A. The incidence is rare, approximately 1 in 1000 patients presenting with ACS
- B. Emotional stress in the presence of symmetric T-wave inversion in most leads is diagnostic for the condition
- C. At angiography, most patients with this condition will not have obstructive CAD
- D. Inotropes in this patient are likely to improve hemodynamics
- E. The condition is more common in women

39-10. A 67-year-old man presents to the emergency department with chest pain and is diagnosed with NSTEMI. According to the 2014 ACCF/AHA guidelines, all of the following represent class III recommendations *except*:

- A. Ibuprofen for early pericarditis
- B. Nitroglycerin for pain relief in a patient with recent sildenafil use
- C. Immediate release nifedipine in the absence of a beta-blocker
- D. Intravenous metoprolol if the oral route is unavailable
- E. Withholding oxygen therapy to when SpO₂ is < 90%

ANSWERS

39-1. The answer is E. (*Hurst’s The Heart, 14th Edition, Chap. 39*) T wave flattening or low-level inversion (< 1 mm) is associated with a lower likelihood of obstructive CAD as the basis for chest symptoms, whereas more marked symmetric T-wave inversion in multiple precordial leads is highly suggestive of CAD. A number of factors increase or decrease the likelihood of CAD ([Table 39-1](#); answers A through D are incorrect).

TABLE 39-1 Likelihood that Chest Symptoms Are Caused by Myocardial Ischemia Attributable to Obstructive Coronary Artery Disease

<p>High likelihood</p> <p>Known coronary disease (particularly recent PCI)</p> <p>Typical angina reproducing prior documented angina</p> <p>Hemodynamic or ECG changes during pain</p> <p>Dynamic ST-segment elevation or depression of ≥1 mm</p> <p>Marked symmetric T-wave inversion in multiple precordial leads</p> <p>Elevated cardiac enzymes in a rising and falling pattern</p> <p>Intermediate likelihood</p> <p>Absence of high-likelihood features and any of the following:</p> <p>Typical angina in a patient without prior documented angina</p> <p>Atypical anginal symptoms in diabetics or in nondiabetics with two or more other risk factors</p> <p>Male gender</p>
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Age older than 70 y
Extracardiac vascular disease
ST depression 0.5-1.0 mm or T-wave inversion of ≥ 1 mm
Low-level troponin elevation that is “flat” and does not rise or fall
Low likelihood
Absence of high- or intermediate-likelihood features but may have:
Chest discomfort reproduced by palpation
T waves flat or inverted < 1 mm
Normal ECG

39-2. The answer is C. (*Hurst’s The Heart, 14th Edition, Chap. 39*) Even minor ST depression is associated with a markedly increased mortality rate. Among 9461 patients enrolled in the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) study, mortality at 30 days was 5.1% in patients with ST-segment depression versus 2.1% among those without ST-segment depression.¹

Transient ST-segment depression of at least 0.5 mm that appears during chest discomfort and disappears after relief provides objective evidence of transient myocardial ischemia. When it is a constant finding with or without chest pain, it is less specific (option A is incorrect). A common but nonspecific ECG pattern in patients with UA/NSTEMI consists of persistent negative T waves over the involved area (option B is incorrect). Deeply negative T waves across the precordial (anterior) leads suggest a proximal, severe, left anterior descending coronary artery stenosis as the culprit lesion and are considered a marker of high risk. However, patients with isolated T-wave inversion have a more favorable prognosis than do those with ST-segment depression (option D is incorrect).²

39-3. The answer is A. (*Hurst’s The Heart, 14th Edition, Chap. 39*) Stress testing is commonly used for risk stratification in patients with UA/NSTEMI who are managed with an initial conservative (“ischemia-guided”) strategy. The Duke treadmill score (DTS) is used to objectify risk during exercise stress testing. The score is calculated as: DTS = Exercise time (minutes) – (5 × ST deviation in mm) – (4 × angina index). The angina index is scored as: 0 points if no angina occurs, 1 point if nonlimiting angina occurs, and 2 points if angina occurs that limits exercise. Scores are considered low (> 5), intermediate (between 4 and -11), and high (< -11). The other answer choices confer a high risk (Table 39-2; options B through E are incorrect). Stress tests should be symptom limited rather than submaximal, and a stress ECG without adjunctive imaging is appropriate unless baseline ECG abnormalities would preclude adequate interpretation. Those with high-risk findings should undergo coronary arteriography; those with negative or low-risk results can be treated medically. Low-risk patients who complete a stay in a chest pain unit without objective evidence of myocardial ischemia can safely undergo stress testing for diagnosis and prognostic purposes either immediately or, when possible, within 48 hours as an outpatient. In patients who cannot exercise, pharmacologic testing with dipyridamole, adenosine, regadenoson, or dobutamine can be used to provide the stress, and sestamibi imaging or echocardiography can be used as a method of assessment.

TABLE 39-2 American College of Cardiology/American Heart Association Noninvasive Risk Stratification

High risk (> 3% annual mortality rate)
1. Severe resting LV dysfunction (LVEF < 0.35)
2. High-risk treadmill (score ≤ 11)
3. Severe exercise LV dysfunction (exercise LVEF < 0.35)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilatation or increased lung uptake
7. Stress-induced moderate perfusion defect with LV dilatation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving > 2 segments) developing at a low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (≤ 120 bpm)
9. Stress echocardiographic evidence of extensive ischemia
Intermediate risk (1%-3% annual mortality rate)
1. Mild to moderate resting LV dysfunction (LVEF 0.35-0.49)
2. Intermediate-risk treadmill score (score -11 to $+5$)
3. Stress-induced moderate perfusion defect without LV dilatation or increased lung intake
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤ 2 segments.
Low risk (< 1% annual mortality rate)
1. Low-risk treadmill (score $\geq +5$)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

- 39-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 39*) The TIMI Risk Score for unstable angina/NSTEMI errs in the risk stratification of patients presenting with suspected acute coronary syndromes. The score allocates points for all of the above risk factors, except for ST changes ≥ 0.5 mm (not 1 mm) on ECG (options A, B, C, and E are incorrect). Patients with unstable angina/NSTEMI at low risk based on TIMI Risk Scores 0 or 1 (or GRACE Risk Score of < 109) can be managed by an "ischemia-guided" strategy.
- 39-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 39*) Although reversible, ticagrelor still has residual antiplatelet effects for up to 5 days among individuals on chronic therapy, and it should be withheld for at least 5 days if possible prior to nonemergent surgery. Ticagrelor has several known, usually self-limited, side effects, which likely arise from its interference with adenosine uptake (options A through C are incorrect). In the PLATO trial,³ at the end of the 12-month follow-up period, the primary end point (CV death, MI, and stroke) was reduced from 11.7% in the clopidogrel arm to 9.8% in the ticagrelor arm (HR, 0.84; 95% CI, 0.77–0.92; $P < .001$). In addition to significant reductions in MI alone, there was also a significant 21% relative risk reduction in vascular mortality and a 22% reduction in total mortality (5.9% vs 4.5%; $P < .001$).
- 39-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 39*) Fondaparinux receives a class I recommendation in the most recent AHA/ACC NSTEMI guidelines. In the OASIS 5 trial, which enrolled $> 20,000$ patients with UA/NSTEMI, 2.5 mg/d of fondaparinux versus 1 mg/kg twice a day of enoxaparin yielded similar rates of the primary end point of death, MI, or refractory ischemia at 9 days (5.8% vs 5.7%; option A is incorrect). However, major bleeding events were reduced by 48% with fondaparinux, and mortality trended lower in the fondaparinux group at 30 days (2.9% vs 3.5%; $P = .02$) and at 180 days (5.8% vs 6.5%; $P = .05$); all but three of the 64 excess deaths with enoxaparin were associated with major or minor bleeding (option B is incorrect). However, several caveats to the OASIS 5 trial merit mention. First, patients were allowed entry with a creatinine up to 3.0 mg/dL. Major bleeding risk was particularly high among patients treated with weight-adjusted enoxaparin who had a creatinine clearance below 30 mL/min (9.9% rate of major bleeding; option D is incorrect). Second, UFH was administered after randomization in a larger proportion of enoxaparin-treated patients, a practice that is thought to increase bleeding risks. Third, the long half-life of fondaparinux may create logistical problems in centers that perform early cardiac catheterization. Finally, among patients undergoing cardiac catheterization, an excess in catheter-related thrombotic complications was observed, a finding that has also been observed in other trials using fondaparinux (option C is incorrect). Finally, it should be noted that, as of the time of writing, fondaparinux has not been approved by the United States Food and Drug Administration for use in patients with acute coronary syndromes, although it received a class I recommendation from the ACCF/AHA Guidelines and is used off-label.
- 39-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 39*) **Figure 39-1** demonstrates the coronary angiogram of a patient with spontaneous coronary artery dissection (SCAD); diffuse irregularity of the left anterior descending artery is noted, along with extension into side branches, including the diagonal artery. SCAD is an increasingly recognized cause of ACS, particularly in women age 30 to 50 years. The pathophysiology of SCAD is unknown; many cases occur in situations such as uncontrolled hypertension, in the puerperium, in those with fibromuscular dysplasia, or as a complication of disorders of collagen integrity, such as Marfan syndrome. The diagnosis of SCAD should be entertained when younger (usually female) patients present with symptoms and signs of acute coronary ischemia in the absence of other risk factors. Diagnostic studies for those with SCAD should be similar to those without the diagnosis; the presence of a coronary dissection plane may be challenging to recognize at the time of coronary angiography, so a high level of suspicion for the presence of the diagnosis should be maintained during such procedures. Standard treatment for SCAD is not established. For many, conservative management may be quite effective, particularly if flow is present in the coronary artery at the time of diagnostic coronary angiography; spontaneous healing of the dissection may be seen at the time of follow-up angiography. Revascularization, by PCI or CABG, is potentially indicated in the presence of an occlusion of a coronary vessel. Given the high prevalence of unrecognized fibromuscular dysplasia in affected patients, some recommend screening for the presence of intracranial aneurysm in those affected by SCAD.
- 39-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 39*) Variant angina, also called Prinzmetal's angina, is characterized by transient marked ST-segment elevation in the absence of plaque rupture and is thought to be caused by coronary spasm, which is usually focal and often at the site of a coronary artery stenosis. It is thought that coronary spasm is a result of abnormalities in endothelial function and nitric oxide activity at sites of coronary spasm.
- Patients with variant angina are often difficult to treat because attacks are unpredictable and often occur without an obvious precipitating factor. NTG relieves variant angina attacks within minutes and should be used promptly; long-acting nitrates are initially effective in preventing variant angina attacks (option D is incorrect). CCBs are very effective in preventing attacks of variant angina (options A and B are incorrect); higher CCB doses are often required. For example, long-acting nifedipine (90 mg/d), diltiazem (360 mg/d), verapamil (480 mg/d), and amlodipine (20 mg/d) are commonly used. Statin therapy is indicated (option C is incorrect), given beneficial effects on endothelial function and the common presence of atherosclerosis underlying focal spasm. There is no documented role for beta-blockers.
- 39-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 39*) **Figure 39-2** demonstrates the characteristic left ventriculogram of a patient with stress cardiomyopathy. Widely recognized as an ACS "mimic," stress cardiomyopathy (also known as "apical ballooning" syndrome or takotsubo cardiomyopathy as a result of the resemblance of the dysfunctional LV to a Japanese octopus pot trap) is found in 1.7% to 2.2% of patients presenting with ACS, and the vast majority ($> 90\%$) are women (option E is correct). Stress cardiomyopathy most often follows an acute emotional stress, such as the death of a loved one, and it may be indistinguishable from a high-risk ACS, with typical angina, rise and fall

of troponin, and onset of heart failure symptoms. Characteristic ECG changes of stress cardiomyopathy include the development of symmetric T-wave inversion in most leads; however, such changes are not specific enough to stress cardiomyopathy to avoid diagnostic coronary angiography (option B is incorrect). At angiography, nonobstructed coronary arteries are the rule (option C is incorrect), along with characteristic myocardial dysfunction of the LV apex, with compensatory basal hyperkinesis. Management of patients with stress cardiomyopathy is typically supportive; patients most often recover rapidly after presentation, though shock at presentation is not uncommon. The use of vasodilating inotropic agents or intra-aortic balloon counterpulsation in those with shock may actually worsen hemodynamics because such treatment may precipitate LV outflow tract obstruction in the context of basal hyperkinesis (option D is incorrect). β -Blockers and ACE inhibitors or ARBs are often used during convalescent periods, but their value in stress cardiomyopathy is unknown.

39-10. The answer is E. (*Hurst’s The Heart, 14th Edition, Chap. 39*) A number of pharmacologic strategies are proposed in patients with unstable angina/NSTEMI, as outlined in [Table 39-3](#) (options A through D are incorrect).

TABLE 39-3 American College of Cardiology/American Heart Association Guideline Recommendations for Early Care of Patients with Suspected Acute Coronary Syndrome Treatment Recommendation Level of Evidence

Treatment		Recommendation	Level of Evidence
Oxygen	Administer supplemental oxygen only with oxygen saturation < 90%, respiratory distress, or other high-risk features for hypoxemia	I	C
Nitrates	Administer sublingual nitroglycerin every 5 minutes \times 3 for continuing ischemic pain and then assess need for IV nitroglycerin	I	C
	Administer IV nitroglycerin for persistent ischemia, HF, or hypertension	I	B
	Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor	III:Harm	B
Analgesic therapy	IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications	IIb	B
	NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization	III:Harm	B
β -Adrenergic blockers	Initiate oral β -blockers within the first 24 hours in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to β -blockade	I	A
	Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for β -blocker therapy with concomitant NSTE-ACS, stabilized HF, and reduced systolic function	I	C
	Reevaluate to determine subsequent eligibility in patients with initial contraindications to β -blockers	I	C
	It is reasonable to continue β -blocker therapy in patients with normal LV function with NSTE-ACS	IIa	C
	IV β -blockers are potentially harmful when risk factors for shock are present	III:Harm	B
Calcium channel blockers	Administer initial therapy with nondihydropyridine calcium channel blockers with recurrent ischemia and contraindications to β -blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval > 0.24 seconds, or second- or third-degree atrioventricular block without a pacemaker	I	B
	Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of β -blocker and nitrates in the absence of contraindications	I	C
	Calcium channel blockers are recommended for ischemic symptoms when β -blockers are not successful, are contraindicated, or cause unacceptable side effects	I	C
	Long-acting calcium channel blockers and nitrates are recommended for patients with coronary artery spasm	I	C
	Immediate-release nifedipine is contraindicated in the absence of a β -blocker	III:Harm	B
Cholesterol management	Initiate or continue high-intensity statin therapy in patients with no contraindications	I	A
	Obtain a fasting lipid profile, preferably within 24 hours	IIa	C

Abbreviations: HF, heart failure; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-segment elevation acute coronary syndrome.
Reproduced with permission from Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol*. 2014 Dec 23;64(24):e139-e228.

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CHAPTER 40

ST-Segment Elevation Myocardial Infarction

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 40-1.** All of the following electrocardiographic findings can potentially support the diagnosis of a myocardial infarction in the presence of a known old left bundle branch block *except*:
- A. Precordial R-wave regression
 - B. ST-segment elevation ≥ 1 mm concordant with the QRS complex
 - C. ST-segment elevation ≥ 5 mm discordant with the QRS
 - D. ST-segment depression ≥ 1 mm in leads V_1 , V_2 , or V_3
 - E. T-wave inversions in the anterior precordial leads
- 40-2.** A 55-year-old man with a history of coronary artery disease is brought to the emergency room with chest pain by his wife. His ECG demonstrates ST-segment elevation. Which of the following is *true* about his initial management?
- A. If he presents to a non-PCI-capable hospital, lytic therapy should be administered promptly, in the absence of contraindications, and the patient should emergently be transferred to a PCI-capable hospital for “facilitated PCI”
 - B. If the patient presents to a PCI-capable hospital, the desired first medical contact (FMC)-to-device time is < 120 minutes
 - C. If the patient presents to a non-PCI-capable hospital, and the anticipated FMC-to-device time, including transfer to a PCI-capable hospital, is < 120 minutes, then the patient should be transferred for primary PCI without receiving fibrinolysis
 - D. When PCI is unavailable, a fibrinolytic should be administered within 90 minutes
 - E. Patients treated successfully with fibrinolysis do not require follow-up angiography
- 40-3.** All of the following are reasons to preferentially transfer a patient with STEMI for primary PCI rather than administer fibrinolytic therapy *except*:
- A. Diagnosis of plaque rupture myocardial infarction in doubt
 - B. Cardiogenic shock
 - C. Suspected aortic dissection
 - D. History of ischemic stroke 6 months prior
 - E. Anticipated FMC-to-device time of 90 minutes, including transfer
- 40-4.** Which of the following is *true* about the administration of fibrinolytic therapy for patients with STEMI?
- A. Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population
 - B. Fibrinolysis and primary PCI are associated with equivalent vessel patency rates
 - C. While there is no mortality benefit associated with primary PCI over fibrinolysis, the lower risk of stroke makes primary PCI the preferred reperfusion strategy in most cases
 - D. Fibrinolysis should generally be considered up to 6 hours following symptoms onset
 - E. There are no circumstances under which fibrinolysis should be administered for patients with ST depressions
- 40-5.** A 56-year-old woman presents with crushing chest pain for 30 minutes. Which of the following 12-lead ECG changes would suggest involvement of the left main coronary artery?
- A. ST-segment elevation in lead V_1 in the setting of inferior myocardial infarction
 - B. ST-segment elevation in leads I, aVL, V_5 , and V_6
 - C. Peaking following by a loss of anterior R waves
 - D. Failure of T waves to invert within 48 hours following the administration of fibrinolysis
 - E. ST elevation in lead aVR greater than or equal to the extent of ST-segment elevation in lead V_1

- 40-6.** A 67-year-old man is admitted with an anterior STEMI, and he undergoes successful reperfusion with primary PCI. His left ventricular ejection fraction is 35%. All of the following represent potential angiotensin-converting enzyme (ACE) inhibitor regimens to begin ideally within the first 24 hours for this patient *except*:
- A. Captopril 6.25 to 12.5 mg 3 times/d to start; titrate to 25 to 50 mg 3 times/d as tolerated
 - B. Lisinopril 2.5 to 5 mg/d to start; titrate to 10 mg/d or higher as tolerated
 - C. Ramipril 2.5 mg twice daily to start; titrate to 5 mg twice daily as tolerated
 - D. Trandolapril test dose 0.5 mg; titrate up to 4 mg daily as tolerated
 - E. Enalaprilat 1 mg/dose IV over a two-hour period, followed by oral enalapril
- 40-7.** Which of the following is *true* about the epidemiology of cardiogenic shock complicating myocardial infarction?
- A. No therapy has meaningfully improved the mortality rate from cardiogenic shock
 - B. The incidence of cardiogenic shock as a result of severe LV dysfunction complicating MI has decreased over time
 - C. No trials have successfully demonstrated improvement in outcomes in patients with cardiogenic shock
 - D. Mortality from cardiogenic shock now is approximately 25%
 - E. None of the above statements are true
- 40-8.** A 52-year-old man presents with myocardial infarction and undergoes placement of a pulmonary artery catheter, which demonstrated a cardiac index of 2.6 L/min/m² and a pulmonary capillary wedge pressure of 22 mm Hg. Which of the following Forrester classifications applies to this patient?
- A. Class I
 - B. Class II
 - C. Class III
 - D. Class IV
 - E. Class V
- 40-9.** A 78-year-old woman presents with chest pain and ST elevation in leads II, III, and aVF. She has ST-segment elevation in lead V4R. Within several minutes of assessment, she becomes progressive hypotensive. The cardiac catheterization team is en route to the hospital. All of the following principles apply to therapy for patients with STEMI and RV infarction and ischemic dysfunction *except*:
- A. Nitroglycerine is beneficial to relieve symptoms of chest pain and to decrease endogenous catecholamine release
 - B. Atrioventricular synchrony should be achieved, and bradycardia should be corrected
 - C. RV preload should be optimized, which usually requires initial volume challenge in patients with hemodynamic instability provided the jugular venous pressure is normal or low
 - D. RV afterload should be optimized, which usually requires therapy for concomitant LV dysfunction
 - E. Inotropic support should be used for hemodynamic instability not responsive to volume challenge
- 40-10.** Which of the following is *true* of patients with acute mitral regurgitation (MR) in the setting of myocardial infarction?
- A. The onset of MR due to papillary muscle is usually 14 days following myocardial infarction
 - B. Acute MR will be detectable at the bedside by the presence of a new-onset, loud, apical systolic murmur
 - C. When papillary muscle rupture occurs, the posteromedial papillary muscle is more often involved than the anterolateral muscle
 - D. Echocardiography is often insufficient to make the diagnosis
 - E. IABP and blood pressure control are used to treat patients acutely and to allow the myocardium to heal; surgery is rarely required

ANSWERS

- 40-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 40*) New-onset (or not known to be old) LBBB in the setting of chest pain is typically considered and treated as an STEMI. Conversely, the diagnosis of STEMI in the setting of old LBBB can be difficult. Findings suggesting STEMI include (1) a pathologic Q wave in leads I, aVL, V₅, or V₆ (two leads); (2) precordial R-wave regression (option A is incorrect); (3) late notching of the S wave in V₁ to V₄; and (4) deviation of the ST segment in the same direction as that of the major QRS deflection.

An analysis of ECG data from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I study identified three criteria for diagnosing myocardial infarction in the presence of the LBBB: (1) ST-segment elevation ≥ 1 mm concordant with the QRS complex; (2) ST-segment depression ≥ 1 mm in leads V₁, V₂, or V₃; and (3) ST-segment elevation ≥ 5 mm discordant with the QRS (options B through D are incorrect).¹ Such findings are often referred to as the Sgarbossa criteria.

- 40-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 40*) Primary PCI is superior to fibrinolytic therapy, and when available should be pursued. Patients who present with STEMI to a non-PCI-capable hospital should receive prompt (< 30 minutes; option D is incorrect) fibrinolytic therapy in the absence of contraindications. Such patients should then usually be transferred to a PCI-capable hospital, where follow-up angiography between 3 and 24 hours later (not sooner; option A is incorrect) can be undertaken. If there is evidence of failed thrombolytic therapy (shock, recurrent chest pain, failure of ST segments to decrease by > 50%), then the patient should be transferred more urgently for PCI. On the other hand, for patients who present with STEMI to a PCI-capable hospital, the desired FMC-to-device (eg, coronary stent) time is < 90 minutes (option B is incorrect).
- 40-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 40*) Patients who present with STEMI to a non-PCI-capable hospital can be managed with fibrinolysis or early transfer to a PCI-capable hospital. If the anticipated FMC-to-device time is anticipated to be < 120 minutes, then transfer should be undertaken (option E is incorrect). Patients presenting with an uncertain diagnosis, such as those with suspected coronary artery dissection, aortic dissection (option C is incorrect), or pericarditis, should be considered for transfer for primary PCI. Additionally, patients with contraindications to fibrinolysis, including ischemic stroke within 3 months (option D is incorrect), should be transferred, as well as those with cardiogenic shock (option B is incorrect).
- 40-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 40*) While the efficacy of reperfusion declines over time, patients with evidence of ongoing ischemia (ie, chest pain or ongoing ECG changes suggestive of ischemia) can be considered for reperfusion, although in this population the efficacy is anticipated to be lower, and primary PCI is preferred over fibrinolysis. Approximately 95% of patients who are treated with primary PCI obtain complete reperfusion versus 50% to 60% of patients who are treated with fibrinolytics (option B is incorrect). Primary PCI is also associated with a lower risk of stroke than treatment with fibrinolysis, and diagnostic angiography quickly defines coronary anatomy, LV function, and mechanical complications. In meta-analyses, primary PCI is associated with a lower mortality rate (7% vs 9%; $P = .0002$), less reinfarction (3% vs 7%; $P = .0001$), and fewer strokes (1% vs 2%; $P = .0004$) at 30 days when compared with fibrinolysis (option C is incorrect).²
- Fibrinolysis should be considered up to 12 hours following symptoms onset (option D is incorrect). Fibrinolytic therapy should not be administered to patients with ST depression, except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR (option E is incorrect).
- 40-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 40*) ST-segment elevation in lead aVR is an ominous sign and is more frequent in patients with left main artery occlusion than in patients with left anterior descending coronary artery or right coronary artery occlusion. In a study of STEMI patients, ST-segment elevation in lead aVR that was greater than or equal to the extent of ST-segment elevation in lead V₁ had 81% accuracy for diagnosing left main occlusion.³ Generally, ST-elevation myocardial infarction is defined by new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mV) in men or 1.5 mm (0.15 mV) in women in leads V₂ to V₃ and/or of 1 mm (0.1 mV) in other contiguous chest leads or the limb leads. ST-segment elevation in lead V₁ in the setting of inferior myocardial infarction suggests RV involvement (option A is incorrect). Because no leads on the standard 12-lead ECG directly represent the posterior myocardium, isolated infarction of this area may be difficult to diagnose but is typically manifested by ST-segment depression in V₁ to V₃, a mirror image of anterior myocardial infarct. ST-elevation in leads I, aVL, V₅, and V₆ suggests lateral wall infarction (option B is incorrect). While the R wave may initially increase in height but then soon decrease, this finding is not specific for left main coronary artery disease (option C is incorrect). Failure of the T wave to invert within 24 to 48 hours suggests early postinfarction regional pericarditis (option D is incorrect).
- 40-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 40*) In the Cooperative New Scandinavian Enalapril Survival Study-2 (CONSENSUS-2) trial, intravenous enalaprilat was administered within 24 hours of presentation followed by oral enalapril. In CONSENSUS-2, mortality was nonsignificantly increased in the treatment group. Conversely, a number of trials demonstrated a benefit with other ACE inhibitor regimens in patients with myocardial infarction, including the Survival and Ventricular Enlargement (SAVE) and Captopril and Thrombolysis Study (CATS) trials of captopril (option A is incorrect), the Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3) trial of lisinopril (option B is incorrect), the Acute Infarction Ramipril Efficacy (AIRE) trial (option C is incorrect), and the Trandolapril Cardiac Evaluation (TRACE) trial (option D is incorrect).
- 40-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 40*) Cardiogenic shock as a result of severe LV dysfunction occurs in approximately 7% of patients with myocardial infarction; it previously had a mortality rate of approximately 80% before the widespread implementation of early revascularization (option A is incorrect). There was a trend toward increased in-hospital survival in the mid- to late 1990s, which correlated with the increased application of reperfusion technologies. The SHOCK II (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock II) trial demonstrated the benefit of early revascularization in patients with MI and cardiogenic shock (option C is incorrect). In most recent studies, the mortality from cardiogenic shock remains approximately 50% (option D is incorrect).
- 40-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 40*) Forrester described the treatment of patients on the basis of hemodynamic subsets related to pulmonary artery wedge pressure and cardiac output ([Table 40-1](#)). The basic goals of this approach include adjustment of the intravascular volume status to bring the pulmonary artery capillary wedge pressure from 18 to 20 mm Hg and optimization of cardiac output with inotropic and/or vasodilating agents. Severely hypotensive patients can be temporarily aided by intra-aortic balloon pumping or possibly by a ventricular assist device.

However, the benefits from these mechanical treatments are often temporary, and there may be a significant risk of complications.

TABLE 40-1 Forrester Classification of Myocardial Infarction

	Cardiac Index (L/min/m ²)	Pulmonary Capillary Wedge Pressure (mm Hg)
Class I	> 2.2	< 18
Class II	> 2.2	> 18
Class III	< 2.2	< 18
Class IV	< 2.2	> 18

- 40-9. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 40*) Patients with right ventricular myocardial infarction should not receive therapies that could deplete preload, such as nitroglycerine. Patients with right ventricular infarction (RVI) present with a mix of left ventricular and right ventricular injury, and the overall balance between the extent of RV and LV dysfunction is a major determinant of long-term outcome. Most patients with RVI and significant hemodynamic compromise have evidence of extensive biventricular infarction and cardiogenic shock. Treatment of RVI initially involves volume loading with normal saline to achieve a pulmonary artery wedge pressure of 18 to 20 mm Hg. In some patients, this alone is sufficient to improve cardiac output and systemic pressure. However, some patients will not respond to fluid loading alone. This may be a result of marked RV enlargement within a relatively noncompliant pericardium, which may result in functional LV compression because of ventricular interaction. In addition to volume loading, the use of dobutamine improves cardiac index. Patients requiring temporary pacing for heart block may also benefit from arteriovenous sequential pacing rather than lone ventricular pacing.
- 40-10. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 40*) Severe MR caused by papillary muscle rupture is responsible for approximately 5% of deaths in AMI patients. Rupture may be complete or partial, and it usually involves the posteromedial papillary muscle because its blood supply is derived only from the posterior descending artery, whereas the anterolateral papillary muscle has a dual blood supply from both the left anterior descending and the circumflex coronary arteries. Most patients have relatively small areas of infarction with poor collaterals, and up to half of the patients may have single-vessel disease. The clinical presentation of papillary muscle rupture is the acute onset of pulmonary edema, usually within 2 to 7 days after inferior myocardial infarction (option A is incorrect). The characteristics of the murmur vary; as a result of a rapid increase of pressure in the left atrium, no murmur may be audible (option B is incorrect). Thus a high degree of suspicion, especially in patients with inferior wall infarction, is necessary for diagnosis. Two-dimensional echocardiographic examination demonstrates the partially or completely severed papillary muscle head and a flail segment of the mitral valve (option D is incorrect). LV function is hyperdynamic as a result of the severe regurgitation into the low-impedance left atrium; this finding alone, in a patient with severe congestive heart failure, should suggest the diagnosis. The cornerstones of successful therapy are prompt diagnosis and emergency surgery (option E is incorrect). Emergent placement of an IABP and blood pressure control may be beneficial. The current approach of emergency surgery accrues an overall operative mortality of 0% to 21%, but this appears to be decreasing, and the late results of this approach can be excellent.

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CHAPTER 41

Antiplatelet and Anticoagulant Therapy in Acute Coronary Syndromes

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 41-1.** A 45-year-old man undergoes coronary stent implantation for stable ischemic heart disease. He is prescribed clopidogrel and aspirin. Which of the following is *true* about his antithrombotic regimen?
- A. The dose of aspirin should be between 75 and 100 mg per day
 - B. Higher doses of aspirin could be more effective at preventing ischemic events, but at the expense of a higher risk of bleeding
 - C. Clinical trials support a higher dose (ie, 300 to 325 mg daily) of aspirin in patients with ischemic heart disease
 - D. When used with newer-generation oral P2Y₁₂ receptor inhibitors (prasugrel and ticagrelor), no preference to aspirin dosing is given
 - E. None of the above
- 41-2.** All of the following are actions of thromboxane A₂ (TXA₂) *except*:
- A. Induces platelet aggregation
 - B. Potent vasoconstrictor
 - C. Regulation of renal blood flow
 - D. Induces proliferation of vascular smooth-muscle cells
 - E. Proatherogenic
- 41-3.** Which of the following is *true* about clopidogrel?
- A. Clopidogrel is approved only in patients receiving percutaneous coronary intervention (PCI) for myocardial infarction
 - B. All patients with ST-elevation myocardial infarction (STEMI) should receive a loading dose of 600 mg of clopidogrel
 - C. Renal dose adjustment in the loading and maintenance dose should be undertaken when the estimated glomerular filtration rate (eGFR) is < 30 mL/min per 1.73 m²
 - D. In patients scheduled for nonemergent coronary artery bypass graft (CABG) surgery, clopidogrel should be held for 5 days if it is safe to do so clinically
 - E. Clopidogrel is a bioactive immediately medication
- 41-4.** Which of the following is *true* about intravenous antiplatelet agents?
- A. Cangrelor is an intravenous adenosine diphosphate (ADP) analog
 - B. Cangrelor requires conversion into a bioactive metabolite in the liver
 - C. Cangrelor's use is experimental only.
 - D. Parenteral glycoprotein IIb/IIIa inhibitors (such as abciximab, eptifibatide, and tirofiban) have demonstrated an evidence-based reduction in major adverse cardiac events in patients undergoing percutaneous coronary intervention
 - E. Thrombocytopenia is uncommon with glycoprotein IIb/IIIa inhibitors
- 41-5.** According to the American College of Cardiology Foundation/American Heart Association guidelines for the use of thrombolytics in the management of ST-segment elevation myocardial infarction, all of the following are true *except*:
- A. In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non-PCI-capable hospitals when the anticipated first medical contact (FMC)-to-device time at a PCI-capable hospital exceeds 90 minutes because of unavoidable delays
 - B. When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival

- C. In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability
- D. Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when it is associated with ST elevation in lead aVR
- E. Fibrin-specific fibrinolytic agents (tenecteplase, reteplase, alteplase) are preferred over streptokinase if available

41-6. All of the following are *true* about aspirin pharmacokinetics *except*:

- A. Peak plasma levels occur 30 to 40 minutes after ingestion
- B. Aspirin absorption in the upper gastrointestinal tract occurs within 60 minutes
- C. Enteric coating of aspirin has negligible effects on absorption pharmacokinetics
- D. COX-mediated TXA₂ synthesis is prevented for the entire life span of the platelet
- E. COX-1 and COX-2 are not similarly blocked by equivalent doses of aspirin

41-7. The following are absolute contraindications to fibrinolytic therapy *except*:

- A. Structural intracranial disease
- B. Previous intracranial hemorrhage
- C. Previous ischemic stroke
- D. Active bleeding or bleeding diathesis
- E. Recent brain or spinal surgery or recent head trauma with fracture or brain injury

41-8. All of the following anticoagulants act by interrupting factor Xa *except*:

- A. Enoxaparin
- B. Fondaparinux
- C. Unfractionated heparin
- D. Rivaroxaban
- E. Bivalirudin

41-9. According to the American College of Cardiology Foundation/American Heart Association guidelines for the use of anticoagulants in the management of ST-segment elevation myocardial infarction, all of the following are true *except*:

- A. Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive enoxaparin administered according to age, weight, and creatinine clearance, given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to 8 days or until revascularization
- B. The recommended dosing for enoxaparin for age < 75 years is 30-mg IV bolus followed by 1 mg/kg SC every 12 h (maximum of 100 mg for the first 2 SC doses) and for age > 75 years is no IV bolus, 0.7 mg/kg SC every 12 h (maximum of 7 mg for the first 2 SC doses)
- C. For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last dose of enoxaparin was given < 8 h before PCI, is recommended no additional anticoagulant therapy. If the last dose of enoxaparin was given 8 to 12 h before PCI, is recommended a 0.3mg/kg bolus of IV enoxaparin at the time of PCI
- D. For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis, weight-based IV bolus and infusion of UFH adjusted to obtain aPTT of 1.5 to 2.0 times control are recommended for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization
- E. All of the above are consistent with recommendations in the guidelines

ANSWERS

41-1. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 41*) While some pharmacodynamic studies have suggested high-dose aspirin (eg, 325 mg) may be associated with enhanced antithrombotic effects as a result of COX-1–independent mechanisms, these pharmacodynamic observations do not appear to translate into improved clinical outcomes, and when given in combination with clopidogrel, the maintenance dose of aspirin should generally be lowered to 75 to 100 mg. This is based on a post hoc analysis of data from the CURE¹ (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study in which similar efficacy but less major bleeding was seen in the low-dose (< 100 mg) aspirin group (option B is incorrect). Furthermore, a large-scale prospective randomized study to compare high- versus low-dose aspirin, the CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes)² trial did not show a benefit to higher dose (300 to 325 mg) versus lower dose (75 to 100 mg) daily aspirin (option C is incorrect). Finally, the introduction into clinical practice of newer-generation oral P2Y₁₂ receptor inhibitors (prasugrel and ticagrelor) that are characterized by greater potency than

clopidogrel and are used in combination with aspirin has also led to questions about the optimal dose of aspirin in these patients. Although aspirin dosing did not affect the safety and efficacy profile of patients treated with prasugrel in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study, a higher dose of aspirin (≥ 300 mg) was associated with reduced efficacy, albeit with no differences in bleeding, in patients treated with ticagrelor in the PLATO (Platelet Inhibition and Outcomes) trial³ (option D is incorrect).

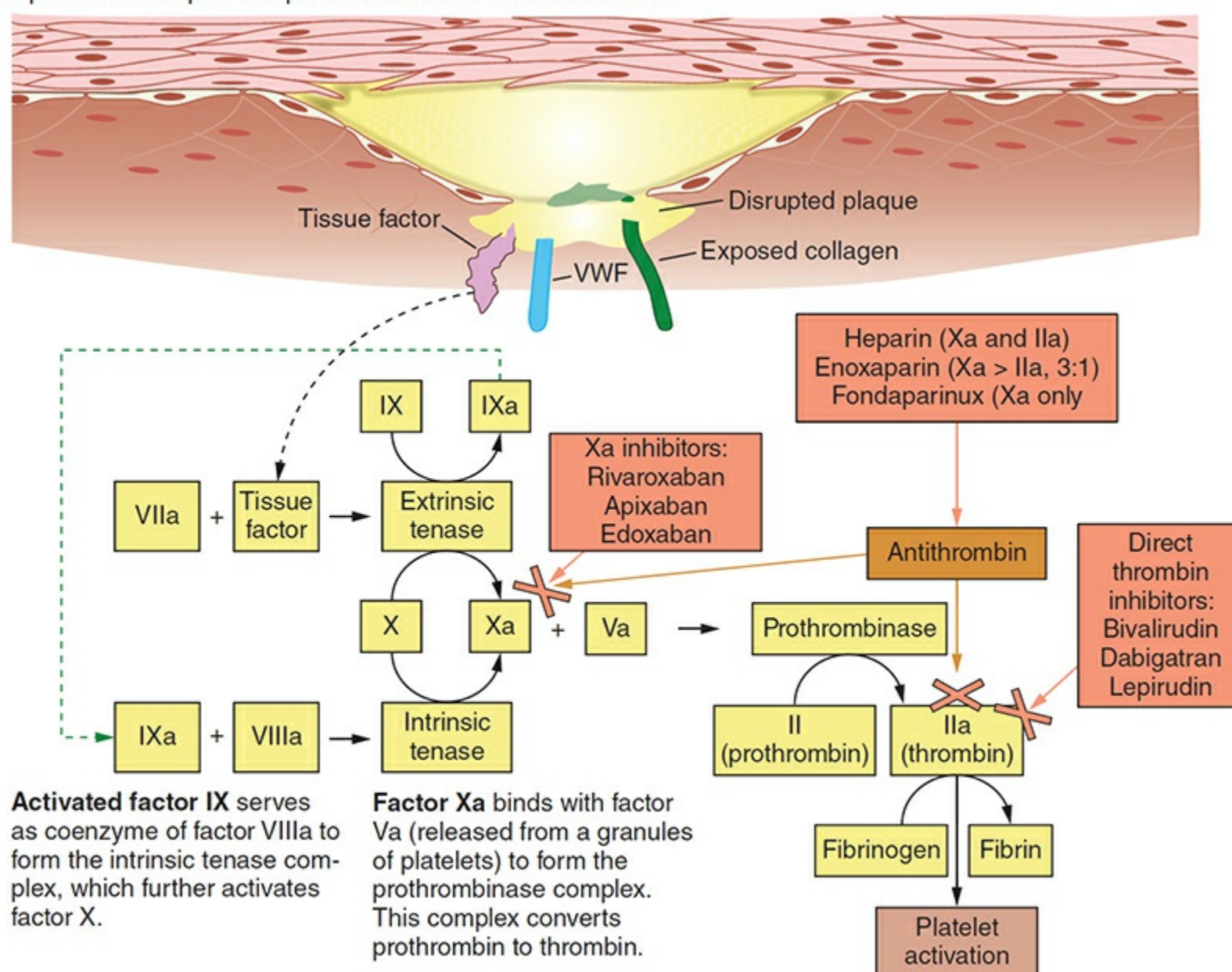
- 41-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 41*) The cyclooxygenase (COX) isozymes catalyze the conversion of arachidonic acid to prostaglandin H_2 , an unstable intermediate that is the substrate for multiple downstream isomerases that lead to the generation of several prostanoids, including TXA_2 and prostacyclin (PGI_2). Thromboxane A_2 plays roles in platelet aggregation, vasoconstriction, the proliferation of vascular smooth-muscle cells, and the acceleration of atherosclerosis (options A, B, D, and E are incorrect). Conversely, prostacyclin plays a role in regulating renal blood flow, and it functions as a platelet inhibitor and a vasodilator. Only COX-1 is expressed in mature platelets. Importantly, TXA_2 (an amplifier of platelet activation and a vasoconstrictor) is derived largely from COX-1 (mostly from platelets), and its biosynthesis is highly sensitive to inhibition by aspirin, whereas vascular PGI_2 (a platelet inhibitor and a vasodilator) is derived predominantly from COX-2 and is less susceptible to inhibition by low doses of aspirin. Therefore, low-dose aspirin ultimately preferentially blocks platelet formation of TXA_2 , diminishing platelet aggregation mediated by thromboxane (TP) receptor pathways.
- 41-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 41*) In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least 5 days in patients receiving clopidogrel. Clopidogrel is approved for the treatment and prevention of secondary atherothrombotic events across the spectrum of patients with ACS, irrespective of the treatment strategy (invasive or noninvasive; option A is incorrect). This recommendation is independent of whether patients are revascularized or not (ie, medical management) and irrespective of strategy for those undergoing PCI (ie, similar for bare metal stent [BMS], drug-eluting stent [DES], or balloon angioplasty). Clopidogrel is also the only oral $P2Y_{12}$ receptor inhibitor approved for patients with stable CAD undergoing PCI. The recommended loading dose of clopidogrel is 300 to 600 mg. However, in the setting of PCI, a 600-mg loading dose is most commonly used. A 300-mg loading dose of clopidogrel, in addition to aspirin, should also be given in patients under age 75 with STEMI treated with fibrinolytic therapy; patients 75 or older treated with fibrinolytic therapy should be treated with clopidogrel 75 mg (without a loading dose; option B is incorrect). After loading dose administration, a maintenance dose of 75 mg daily should be initiated. No dosage adjustment is necessary for patients with renal impairment, including patients with end-stage renal disease (option D is incorrect). Clopidogrel is an inactive prodrug that requires oxidation by the CYP system to generate an active metabolite (option E is incorrect).
- 41-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 41*) Glycoprotein IIb/IIIa inhibitors (GPIs) have been shown to reduce major adverse cardiac events (death, MI, and urgent revascularization) by 35% to 50% in patients undergoing PCI. However, their broad use has been limited because they are associated with an increased risk of bleeding complications. Moreover, their use has declined in recent years because of treatment alternatives, such as bivalirudin, associated with a more favorable safety profile (ie, less bleeding) as well as the introduction of potent $P2Y_{12}$ receptor inhibitors. Cangrelor is an intravenous adenosine triphosphate (ATP) analog (option A is incorrect). Due to structural modifications, cangrelor has high affinity for the $P2Y_{12}$ receptor and a higher resistance to ectonucleotidases, does not require hepatic conversion, and is directly active (option B is incorrect). Cangrelor was approved by the FDA in 2015 as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet receptor inhibitor and are not being given a GPI (option C is incorrect).
- Acute coronary syndrome trials tended to report higher incidence of thrombocytopenia among patients treated with abciximab compared with PCI trials (option E is incorrect). Some of this risk may be mediated by the need for longer heparin infusions and an increased risk of heparin-induced thrombocytopenia (HIT). Eptifibatide or tirofiban does not appear to increase mild or severe thrombocytopenia compared with placebo. Severe and profound ($< 20,000$) thrombocytopenia is more commonly associated with abciximab use and requires immediate cessation of therapy. Pseudothrombocytopenia secondary to platelet clumping and HIT needs to be ruled out. The platelet count returns to normal within 48 to 72 hours in most cases.
- 41-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 41*) In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non-PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. The remainder of the statements provided are correct (options B through E are incorrect).
- 41-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 41*) Enteric-coated aspirin delays absorption, with peak plasma levels at 3 to 4 hours, as opposed to 30 to 40 minutes for non-enteric coated (option A is incorrect). Aspirin is rapidly absorbed in the upper gastrointestinal tract and is associated with measurable platelet inhibition within 60 minutes (option B is incorrect). Because the blockade of COX-1 induced by aspirin is irreversible, COX-mediated TXA_2 synthesis is prevented for the entire life span of the platelet (about 7 to 10 days; option D is incorrect). Therefore, even low doses of aspirin can produce long-lasting platelet inhibition. Higher doses of aspirin are needed to inhibit COX-2 than to inhibit COX-1 (option E is incorrect). These differences explain why very high doses of aspirin are needed to

achieve anti-inflammatory and analgesic effects, whereas low doses of aspirin lead to antiplatelet effects.

- 41-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 41*) Ischemic stroke within the past 3 months is an absolute contraindication to fibrinolytic therapy; ischemic stroke > 3 months prior is a relative contraindication only. The remainder of the options provided are absolute contraindications to fibrinolytic therapy (options A, B, D, and E are incorrect). In addition to ischemic stroke > 3 months prior, other relative contraindications include: systolic blood pressure > 180 or diastolic blood pressure > 110 mm Hg, recent bleeding (nonintracranial), recent surgery, recent invasive procedure, anticoagulation (eg, vitamin K therapy), traumatic or prolonged cardiopulmonary resuscitation, pericarditis or pericardial fluid, and diabetic retinopathy, among others.
- 41-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 41*) Anticoagulants act by antagonizing or synergizing various factors along the clotting cascade (**Figure 41-1**). Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X. Activated factor IX serves as a coenzyme of factor VIIIa to form the intrinsic tenase complex, which further activates factor X. Factor Xa binds with factor Va (released from granules of platelets) to form the prothrombinase complex. This complex converts prothrombin to thrombin. Thrombin is a powerful stimulant of platelet activator, further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot. Factor Xa is antagonized either directly (rivaroxaban, apixaban, or edoxaban; option D is incorrect) or indirectly by agents that synergize antithrombin (unfractionated heparin, enoxaparin, and fondaparinux; options A through C are incorrect). Conversely, direct thrombin inhibitors, including bivalirudin, dabigatran, and lepirudin act to block thrombin (factor IIa) directly.

Coagulation cascade and site of action of various anticoagulants

Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X.



Thrombin is a powerful stimulant of platelet activator (via PAR 1), further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot.

FIGURE 41-1 Coagulation cascade and site of action of various anticoagulants. Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X. Activated factor IX serves as a coenzyme of factor VIIIa to form the intrinsic tenase complex, which further activates factor X. Factor Xa binds with factor Va (released from a granules of platelets) to form the prothrombinase complex. This complex converts prothrombin to thrombin. Thrombin is a powerful stimulant of platelet activator, further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot.

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41-9. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 41*) All of the options above are consistent with American College of Cardiology Foundation/American Heart Association recommendations as of 2017 (options A through D are incorrect).

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CHAPTER 42

Percutaneous Coronary Interventions in Acute Myocardial Infarction and Acute Coronary Syndromes

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 42-1.** Which of the following is *not* an advantage of primary percutaneous coronary intervention (PCI) over fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI)?
- A. Primary PCI is associated with a reduced incidence of intracranial hemorrhage
 - B. Primary PCI is superior in reducing short-term mortality
 - C. Primary PCI has a lower overall risk of major bleeding
 - D. Primary PCI is associated with fewer nonfatal reinfarctions
 - E. All of the above are correct
- 42-2.** A 58-year-old man begins to experience chest pain that radiates to his left arm while jogging. He initially dismisses the symptoms and is admitted to the emergency department 6 hours later with an anterior myocardial infarction (MI) confirmed by ECG. Which of the following may be associated with smaller infarct size?
- A. TIMI grade 1 flow in the infarct artery
 - B. Remote ischemic conditioning
 - C. Anterior MI location
 - D. Reperfusion with PCI at 6 hours
 - E. None of the above
- 42-3.** A 64-year-old woman with long-standing hypertension is admitted to the hospital with an anterior myocardial infarction. She is promptly reperfused by primary PCI, including stenting of the left anterior descending coronary artery. Which of the following are associated with reduced infarct size?
- A. Baseline TIMI grade 3 flow
 - B. Total ischemia time < 3 hours
 - C. Nonanterior MI location
 - D. Remote ischemic conditioning
 - E. All of the above
- 42-4.** A 54-year-old woman presents with an anterior STEMI. Which of the following is *not true* about ticagrelor administration in this patient?
- A. Ticagrelor is an oral P2Y₁₂ inhibitor
 - B. Ticagrelor is not inferior to clopidogrel in the treatment of patients with STEMI
 - C. The rates of stent thrombosis are similar with ticagrelor and clopidogrel
 - D. Crushed oral ticagrelor can increase the time to onset of platelet inhibition
 - E. Dyspnea is a frequent reason for switching from ticagrelor to clopidogrel
- 42-5.** A 48-year-old man presents with an anterior MI and is found to have complete occlusion of the left anterior descending (LAD) artery, as well as an 80% stenosis in the mid-right coronary artery. He is hemodynamically stable and chest pain free following PCI of the LAD. Which of the following is *correct* about the treatment of multivessel disease?
- A. PCI of the infarct artery only has better clinical outcomes than multivessel PCI
 - B. Primary angioplasty of stenosed vessels with normal blood flow is associated with worse survival
 - C. Multivessel PCI is associated with increased cardiac mortality
 - D. Multivessel PCI in the setting of MI is associated with decreased major adverse cardiovascular events

E. All of the above

42-6. Which of the following is *incorrect* regarding adjunctive thrombectomy methods?

- A. Adjunctive aspiration thrombectomy enhances angiographic blush scores and ST-segment resolution
- B. Routine thrombectomy before or after stent implantation enhances outcomes for all thrombi sizes
- C. There is no benefit to the routine use of rheolytic thrombectomy with primary PCI for STEMI
- D. It is reasonable to consider adjunctive thrombectomy in all patients with angiographically large thrombus burden before primary PCI
- E. None of the above are incorrect

42-7. Which of the following constitutes a *correct* sequence of events following the arrival of a STEMI patient to the hospital?

- A. 12-lead ECG, heparin and P2Y₁₂ inhibitor administration, transfer to catheterization lab, revascularization with DES, aspirin treatment indefinitely
- B. 12-lead ECG, discontinue anticoagulation, transfer to catheterization lab, routine thrombectomy and PCI, aspirin treatment indefinitely
- C. Remote ischemic conditioning, 12-lead ECG, transfer to catheterization lab, revascularization with DES, aspirin treatment indefinitely
- D. 12-lead ECG, transfer to catheterization lab, revascularization with DES, heparin and P2Y₁₂ administration
- E. None of the above are correct

42-8. A 44-year-old man presents to the hospital with ongoing acute chest pain and ST depressions on ECG. He has elevated troponin and a history of coronary artery disease. Which treatment is most appropriate for this patient?

- A. “Cool off” the acute thrombotic lesion with antiplatelet and anticoagulant agents for a few days
- B. Coronary angiography performed the next working day
- C. Immediate Coronary angiography
- D. Noninvasive stress testing when troponin is down-trending
- E. None of the above

42-9. A 53-year-old woman is admitted with acute chest pain and ECG signs of non–ST-segment elevation MI. Revascularization the following morning is planned. Which of the following adjunctive pharmacological strategies is *incorrect*?

- A. Pre-PCI treatment with clopidogrel
- B. Aspirin loading dose of 300 to 325 mg
- C. Subcutaneous injection of low-molecular-weight heparin
- D. Pre-PCI treatment with prasugrel
- E. All of the above

42-10. A 70-year-old man is brought to the emergency department with acute chest pain, ST-segment depressions on ECG, and sinus bradycardia. Which adjunctive therapy is *not* appropriate in this patient?

- A. IV nitroglycerin
- B. Beta-blockers
- C. Statin
- D. Oxygen therapy
- E. Dual antiplatelet therapy

ANSWERS

42-1. The answer is C. (*Hurst’s The Heart, 14th Edition, Chap. 42*) Over the past 40 years, improvements in the design and development of highly effective antithrombotic and antiplatelet therapy have made PCI a widely used revascularization strategy. This technique gained particular success as it became apparent that a severe residual stenosis persisted in most patients after successful fibrinolysis treatment. A meta-analysis of 23 randomized trials incorporating 7739 patients compared primary PCI with fibrinolytic therapy for STEMI.¹ Primary PCI was superior to fibrinolytic therapy in reducing short-term mortality (option B), nonfatal reinfarction (option D), stroke, and the composite end point of death, nonfatal reinfarction, and stroke. These results were maintained at long-term follow-up and were independent of the type of thrombolytic agent used (streptokinase vs fibrin-specific thrombolytics) and whether patients were directly admitted or transferred emergently for primary PCI. The incidence of intracranial hemorrhage was significantly less with primary PCI (option A), although the overall risk of major bleeding (mostly related to access site bleeding) was not lower with primary PCI (option C).

42-2. The answer is B. (*Hurst’s The Heart, 14th Edition, Chap. 42*) Once consensus was reached that primary PCI is the superior reperfusion modality, attention turned to limiting infarction size. The last decade has seen many pharmacologic and mechanical strategies to limit infarct size, which are summarized in [Table 42-1](#). Achieving TIMI grade 3 flow has a major impact on short- and long-term mortality. Indeed, there appears to be an inverse relationship between the ability to achieve TIMI grade 3 flow and short-term mortality with either reperfusion strategy (option A). Infarctions involving the LAD artery tend to be larger than left circumflex or right coronary artery infarcts (option C). Symptom onset to balloon time was critically important at up to 3 hours of symptom duration. After 3 hours, MI size did not appear to vary with prolonged times to reperfusion (option D). Experimental models suggest that remote ischemic conditioning, such as transient intermittent limb ischemia, may reduce myocardial infarct size in ischemia-reperfusion models (option B); studies are ongoing.

TABLE 42-1 Infarct Size Reduction.

Proven
1. Baseline TIMI grade 3 flow
2. Total ischemia time < 3 hours
3. Nonanterior MI location
4. Remote ischemic conditioning
Potentially useful in anterior STEMI
1. IV metoprolol
2. SSA O ₂
3. IV adenosine (high dose, early treatment)
4. Hypothermia
Ongoing trials
1. LV unloading
2. Steroids
3. Colchicine

Methods or factors associated with small final infarction size are tabulated. Remote ischemic conditioning is the only therapy to appear to decrease MI size and provide lasting clinical benefit.
Abbreviations: IV, intravenous; LV, left ventricular; MI, myocardial infarction; SSA O₂, hyperoxemic oxygen therapy; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

42-3. The answer is E. (*Hurst’s The Heart, 14th Edition, Chap. 42*) In addition to proven approaches to reducing infarct size (options A–D), several experimental approaches are currently under development, such as methods to decrease reperfusion injury.² Reperfusion injury refers to damage to the myocardial tissue caused when blood supply returns to the tissues after a period of ischemia. In this situation, the restoration of flow results in inflammation and oxidative stress damage. Adenosine can potentially reduce reperfusion injury by suppressing free radical formation and by preventing neutrophil activation. Intracoronary administration of supersaturated oxygen with an arterial oxygen partial pressure of 760 to 1000 mm Hg has been tested in two clinical trials.^{3,4} Patients with anterior MI who were treated with less than 6 hours of symptom duration or a 90-minute selective intracoronary infusion of supersaturated oxygen after PCI had a reduction in infarct size. In addition, many experimental studies have documented the effectiveness of systemic hypothermia, initiated before reperfusion, in reducing infarct size. More recently, two small trials have pooled results and demonstrated a reduction of infarct size and a decrease in heart failure for anterior MI. Finally, IV metoprolol has been shown to reduce infarct size in patients with anterior MI presenting < 6 hours after symptom onset, although currently due to the findings from the COMMIT-CCS2 trial, its routine use in STEMI is not recommended.

42-4. The answer is A. (*Hurst’s The Heart, 14th Edition, Chap. 42*) Ticagrelor is a rapid oral P2Y₁₂ inhibitor (option A). Oral ticagrelor has been compared to clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial. A total of 18,624 patients with AMI and ACS PCI were randomized to clopidogrel 300 mg or ticagrelor 90 mg loading dose and subsequent therapy of 90 mg twice a day. A total of 7008 patients (37%) were undergoing STEMI intervention. The ticagrelor group had a lower event rate (9.8% vs 11.7%; *P* < .0001; option B). Stent thrombosis was decreased from 3.8% to 2.9% (*P* = .01; option C). An even more rapid onset of platelet inhibition can be achieved by crushing the ticagrelor tablet for oral administration (option D). Time to maximal plasma concentration decreased from 4 to 2 hours, and substantial platelet inhibition occurred within 1 hour of oral administration. Dyspnea is a potential complication of ticagrelor, potentially due to its effects on adenosine reuptake, but this side effect is usually self-limited (option E).

42-5. The answer is D. (*Hurst’s The Heart, 14th Edition, Chap. 42*) In initial trials of primary PCTA, plaque dissection and intraluminal thrombosis were difficult to treat with balloon angioplasty and heparin alone. Reocclusion of the infarct-related artery occurred in 5% to 15% of cases and worsened survival. In this context, treating non-culprit stenoses with normal blood flow was considered harmful, and thus the practice of primary angioplasty evolved with treatment of the infarct artery only. However, as antithrombotic, antiplatelet, and coronary stenting improved, the issue of complete revascularization was again raised. Three recently performed well-done randomized trials⁶⁻⁸ demonstrated that the primary end point of death, recurrent MI, or refractory angina was lower in the multivessel PCI group (option A). Cardiac mortality was also lower (option C). They also showed that major adverse cardiovascular events (MACEs) were lower in patients assigned to multivessel PCI (option D) and that on a background of high usage of P2Y₁₂ inhibitors,

multivessel PCI is safe and is associated with improved clinical outcomes compared with culprit-only revascularization.

- 42-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 42*) Primary PCI is effective in restoring normal epicardial coronary flow (TIMI grade 3 flow) in more than 90% of patients with STEMI, but more than half of these patients will have suboptimal flow at the tissue level, as evidenced by poor angiographic blush scores or lack of complete ECG ST-segment resolution. The AIMI (rheolytic thrombectomy) study investigators demonstrated that there is no indication for the routine use of rheolytic thrombectomy with primary PCI for STEMI (option C). However, patients with large thrombus burden often have distal macroembolization, and studies have shown that macroembolization is harmful and leads to impaired myocardial reperfusion and worse clinical outcomes. Therefore, it may be reasonable to consider adjunctive thrombectomy in patients with angiographically large thrombus burden before primary PCI (option D). In another trial involving 1071 patients with STEMI, adjunctive aspiration resulted in enhanced rates of normal angiographic myocardial perfusion (blush) and ST-segment resolution (option A). However, the initial enthusiasm for routine use of aspiration thrombectomy has been dramatically tempered by findings that rates of mortality, TVR, recurrent MI, and stent thrombosis were the same for thrombectomy and primary PCI patients. Only stroke was different and higher in the thrombectomy patients. Thus, routine thrombectomy does not enhance outcomes and should be reserved for large thrombus burden before or after stent implantation (option B).
- 42-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 42*) Regardless of mode of presentation, rapid performance and competent analysis of the 12-lead ECG are the first steps. Skilled reading either on site or by transmission is essential so that “false activations” can be limited. Once a firm diagnosis of STEMI is made, activation of the STEMI team and transport to the catheterization lab are essential. A heparin bolus and a P2Y₁₂ inhibitor should be rapidly administered. If logistically feasible, consideration should be given to remote ischemic conditioning while en route to the catheterization lab. Once the infarct artery is identified, intracoronary abciximab may be considered if not already administered. Routine thrombectomy is not useful, but if extensive clot burden exists, it will prevent extensive macroembolization. The use of DESs should be routine. Proper sizing and proper stent opposition are essential to prevent stent thrombosis, and intravascular ultrasound-guided implantation should be strongly considered. After the procedure, anticoagulation is discontinued unless there are other reasons to resume it. All patients without contraindications should be treated with aspirin indefinitely following PCI. The correct sequence of events is therefore described in option A.
- 42-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 42*) Most patients with non-ST-segment elevation (NSTEMI)-ACS in the United States undergo cardiac catheterization. The evidence for invasive management is based on several randomized trials that showed improvement in MACE, improved symptoms, improved quality of life, and reduction in readmission. The benefits were greater in patients with higher risk (ie, elevated biomarker, ST-segment changes, higher TIMI or GRACE risk scores).⁹ The timing of catheterization has been evaluated in randomized and observational trials. Initially, it was thought that it may be beneficial to “cool off” an ulcerated thrombotic lesion with antiplatelet and anticoagulant agents for a few days (option A). However studies found that earlier intervention is better, particularly in higher-risk patients (option C). Early catheterization was also associated with a reduction in death or large MI at 30 days (option B), and studies consistently favor early invasive strategies over conservative strategies in high-risk patients (option D). In this patient, the presence of ongoing chest pain and the absence of contraindications call for immediate angiography.
- 42-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 42*) The primary goal of pharmacotherapy for NSTEMI-ACS is to alleviate ischemia using antiplatelets, antithrombotics, and adjunctive therapies to reduce myocardial oxygen demand. Pharmacotherapy in NSTEMI-ACS is crucial for management because a substantial portion of patients will not immediately undergo coronary angiography and/or revascularization. Evidence-based guidelines universally advocate that patients with NSTEMI-ACS should routinely and indefinitely receive low-dose (75 to 100 mg) non-enteric-coated aspirin, after an initial loading dose of 300 to 325 mg (option B). Aspirin is routinely given to all patients with CAD, and it is assumed to equally benefit those undergoing and not undergoing an invasive management strategy.^{10,11} The administration of clopidogrel prior to PCI is known to improve outcomes (option A). A study revealed that patients who received pre-PCI treatment with clopidogrel had reduced cardiovascular death, MI, and stent thrombosis when compared with placebo.¹² This can be explained by clopidogrel's slow onset, which is circumvented by early administration. In another trial, pretreatment with prasugrel did not decrease ischemic complications when compared with administration at the time of PCI and was associated with a higher risk for major bleeding.¹³ Prasugrel has a very fast onset, thereby rendering pretreatment unnecessary; clinical trials therefore examined its efficacy by administering it at the time of coronary angiography (option D). Finally, anticoagulation is recommended for all NSTEMI-ACS patients undergoing PCI at the time of diagnosis (class I practice guideline).¹¹ This is typically administered as an IV infusion of UFH or a subcutaneous injection of low-molecular-weight heparin, or in some countries as subcutaneous fondaparinux (option C).
- 42-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 42*) In addition to antiplatelets and antithrombotics, adjunctive therapy with oxygen (options D and E are incorrect) is empirically administered in all patients, and especially for patients with oxygen saturation < 90%. If patients are experiencing ischemic chest discomfort, sublingual or IV nitroglycerin can be used (option A is incorrect). Oral beta-blockade should be initiated within 24 hours to reduce heart rate, contractility, and blood pressure, as long as patients are not experiencing heart failure or low output, are at increased risk of cardiogenic shock, or have other contraindications to beta-blockade such as bradycardia or wheezing (option B is correct).¹⁴ Nondihydropyridine calcium channel blockers can be administered to reduce myocardial oxygen demand if beta-blockers are contraindicated, but they would not be indicated here due to bradycardia. Lastly, high-intensity statin

therapy (option C is incorrect) should be administered as soon as possible in patients presenting with NSTEMI-ACS because it has been associated with reduced rates of recurrent MI, coronary heart disease mortality, need for revascularization, and stroke.¹⁵

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CHAPTER 43

The Evaluation and Management of Stable Ischemic Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 43-1.** A 65-year-old man with a history of obstructive coronary artery disease (CAD) is evaluated in your clinic. He complains that he develops chest pain walking approximately one city block and climbing one flight of stairs. Which of the following Canadian Cardiovascular Society (CCS) angina classes best describes the patient's symptoms?
- A. CCS I
 - B. CCS II
 - C. CCS III
 - D. CCS IV
 - E. None of the above are correct
- 43-2.** All of the following are criteria for defining vulnerable plaque *except*:
- A. Active inflammation (eg, monocyte, macrophage, \pm T-cell infiltration)
 - B. Thin cap with large lipid core
 - C. Endothelial denudation with superficial platelet aggregation
 - D. Fissured plaque
 - E. Luminal stenosis $> 60\%$
- 43-3.** A 64-year-old woman presents to your clinic with progressive exertional chest pressure over the past several months. All of the following are advantages of stress echocardiography over stress myocardial perfusion imaging *except*:
- A. Higher specificity
 - B. Versatility; more extensive evaluation of cardiac anatomy and function
 - C. Greater convenience/efficacy/availability
 - D. Lower cost
 - E. Higher sensitivity, especially for single-vessel coronary disease involving the left circumflex artery
- 43-4.** A 54-year-old woman is evaluated for chest pain and dyspnea with noninvasive testing. Which of the following is *not* considered a high-risk finding?
- A. Severe resting LV dysfunction (LVEF $< 35\%$) not readily explained by noncoronary causes
 - B. Resting perfusion abnormalities $\geq 10\%$ of the myocardium in patients without prior history or evidence of MI
 - C. Stress ECG findings including ≥ 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
 - D. Severe stress-induced LV dysfunction (peak exercise LVEF $< 45\%$ or drop in LVEF with stress $\geq 10\%$)
 - E. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating one vascular territory with abnormalities but without LV dilation
- 43-5.** A 56-year-old man undergoes coronary angiography and is found to have a 70% left main coronary artery (LMCA) stenosis. Which of the following factors would suggest similar efficacy between coronary stenting and coronary artery bypass surgery?
- A. Comorbid diabetes mellitus
 - B. Additional lesions involving the right coronary artery
 - C. Left main stenosis involving calcified plaque at the bifurcation of the LAD and LCx arteries
 - D. Reduced ejection fraction

E. SYNTAX score of 20

43-6. All of the following are key angiographic features important for calculating the SYNTAX score *except*:

- A. Right, left, or codominant coronary circulation
- B. Number of atherosclerotic lesions
- C. Number of artery segments involved per atherosclerotic lesion
- D. Trifurcation lesion: number of vessel segments diseased
- E. All of the above

43-7. Which of the following is *not true* about coronary calcium scoring?

- A. Calcification observed on cardiac CT correlates inversely with the overall extent of CAD
- B. The coronary artery calcification score is a quantitative measure of overall vascular calcium burden
- C. Coronary calcium does not correlate with the degree of luminal obstruction
- D. The overall burden may predict future coronary heart disease events
- E. Serial screening of patients for progression of CAC is not recommended

43-8. Which of the following are core components of a cardiac rehabilitation/secondary prevention program?

- A. Nutritional counseling
- B. Blood pressure management
- C. Tobacco cessation
- D. Lipid management
- E. All of the above

43-9. Which of the following is *incorrect* about patients with human immunodeficiency virus (HIV) and cardiac disease?

- A. Highly active antiretroviral therapy (HAART) is considered a risk factor for CAD
- B. Compared to HIV-negative patients, the prevalence of noncalcified coronary plaques is approximately threefold higher in HIV-positive patients on HAART therapy
- C. The risk of incident MI is increased approximately fourfold among those with HIV
- D. Lipodystrophy is unlikely to mediate the relationship between HIV and CAD
- E. In selected HIV patients at elevated risk for cardiovascular disease, protease inhibitors may be inappropriate

43-10. A 70-year-old man with hypertension is seen in your clinic. Which of the following is *not true* about blood pressure control and the risk of cardiac events?

- A. In patients with stable ischemic heart disease, hypertension is a risk factor for recurrent MI
- B. In patients with diabetes, uncontrolled hypertension is a strong predictor of premature death, cardiovascular morbidity, and progressive nephropathy
- C. Compared to a standard treatment goal SBP < 140 mm Hg, patients treated to intensive blood pressure targets (SBP < 120 mm Hg) have a lower risk for the combination of MI, other ACSs, stroke, HF, and death from cardiovascular causes
- D. Blood pressure control in the elderly need not be as rigorous as in younger patients
- E. Blood pressure control is an important preventive strategy for incident heart failure

ANSWERS

43-1. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 43*) Canadian Cardiovascular Society (CCS) angina classification is described in [Table 43-1](#). This patient's symptoms are most consistent with class III (option C).

TABLE 43-1 The Canadian Cardiovascular Society Angina Scale

I	II	III	IV
Ordinary physical activity does not cause angina including: Walking and climbing stairs	Slight limitation of ordinary activity including: Walking stairs rapidly Walking uphill Stair climbing after meals	Marked limitation of ordinary physical activity.	Inability to perform any physical activity without discomfort.
<i>Angina occurs:</i> Only with strenuous, rapid, or prolonged exertion at work or recreation	<i>Angina occurs:</i> A few hours after awakening Walking > 2 city blocks (level ground) Walking 1 flight of ordinary stairs at a normal pace	<i>Angina occurs:</i> Walking ≤ 1 city block (level ground) Climbing one flight of stairs under normal conditions and at a normal pace	<i>Angina occurs:</i> With minimal activity May be present at rest

Data from Campeau L. The Canadian Cardiovascular Society grading of stable angina pectoris after a quarter of a century of use, *Can J Cardiol.* 2002 Sep;18(9):941-944.

- 43-2. **The answer is E.** (*Hurst’s The Heart, 14th Edition, Chap. 43*) Major criteria for the defining vulnerable plaque include options A through D.¹ Additionally, luminal stenosis > 90% is also a major criterion. Minor criteria include: superficial calcified nodule, glistening yellow appearance (pathologic diagnosis), intraplaque hemorrhage, outward remodeling, and endothelial dysfunction.
- 43-3. **The answer is E.** (*Hurst’s The Heart, 14th Edition, Chap. 43*) Advantages of echocardiography (options A through D) are outlined. Conversely, advantages of stress myocardial perfusion imaging include: higher technical success rate; higher sensitivity, especially for single-vessel coronary disease involving the left circumflex artery (option E); better accuracy for evaluating possible ischemia when multiple resting left ventricular wall motion abnormalities are present; and more extensive published database, especially in the evaluation of the prognosis.²
- 43-4. **The answer is E.** (*Hurst’s The Heart, 14th Edition, Chap. 43*) High-risk findings on noninvasive testing include options A through D, as well as: stress-induced perfusion abnormalities encumbering ≥ 10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities; stress-induced LV dilation; inducible wall motion abnormality (involving > 2 segments or 2 coronary beds); wall motion abnormality developing at a low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min); coronary artery calcium score > 400 Agatston units; and multivessel obstructive CAD (≥ 70% stenosis) or left main stenosis (≥ 50% stenosis) on coronary CT angiography (Table 43-2). Other features are considered low risk, or moderate risk, such as stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating one vascular territory with abnormalities but without LV dilation (option E).

TABLE 43-2 Noninvasive Risk Stratification of Coronary Artery Disease

High risk (> 3% annual death or MI)

1. Severe resting LV dysfunction (LVEF < 35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities $\geq 10\%$ of the myocardium in patients without prior history or evidence of MI
3. Stress ECG findings including ≥ 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF < 45% or drop in LVEF with stress $\geq 10\%$)
5. Stress-induced perfusion abnormalities encumbering $\geq 10\%$ myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving > 2 segments or 2 coronary beds)
8. Wall motion abnormality developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min)
9. CAC score > 400 Agatston units
10. Multivessel obstructive CAD ($\geq 70\%$ stenosis) or left main stenosis ($\geq 50\%$ stenosis) on CCTA

Intermediate risk (1% to 3% annual death or MI)

1. Mild/moderate resting LV dysfunction (LVEF 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities in 5% to 9.9% of the myocardium in patients without a history or prior evidence of MI
3. ≥ 1 mm of ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1 to 2 segments and only 1 coronary bed
6. CAC score 100 to 399 Agatston units
7. One vessel CAD with $\geq 70\%$ stenosis or moderate CAD stenosis (50% to 69% stenosis) in ≥ 2 arteries on CCTA

Low risk (< 1% annual death or MI)

1. Low-risk treadmill score (score ≥ 5) or no new ST segment changes or exercise-induced chest pain symptoms; when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering < 5% of the myocardium*
3. Normal stress or no change of limited resting wall motion abnormalities during stress
4. CAC score < 100 Agatston units
5. No coronary stenosis > 50% on CCTA

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; EEG, electrocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Reproduced with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

43-5. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 43*) A number of factors are associated with benefit from coronary artery bypass over coronary stenting (options A through D). However, in individuals without such factors, and who have favorable anatomy (option E), disease involving the LMCA can be managed with coronary artery stenting or bypass with similar efficacy ([Figure 43-1](#)). Among the strengths of the SYNTAX trial was the use of a numerical score for the objective evaluation of coronary disease severity and the likelihood of revascularization success. The SYNTAX score is generated by summarizing various qualitative plaque features and stenosis locations, and it serves as an objective measure of coronary disease severity that can be used to stratify anticipated patient outcomes (see syntaxscore.com).³ Patients with high (≥ 33) and intermediate (23–32) SYNTAX scores had lower rates of MACCEs with surgery compared with PCI out to 5 years (high SYNTAX score: 26.8% surgery versus 44.0% PCI; $P < .0001$; intermediate SYNTAX score: 25.8% surgery vs 36.0% PCI). Event rates were similar for patients with low SYNTAX scores (≤ 22). The trial also established that PCI is noninferior to bypass surgery for the treatment of left main CAD (31.0% MACCE rate in the CABG surgery group versus 36.9% in the PCI group; $P = .12$).

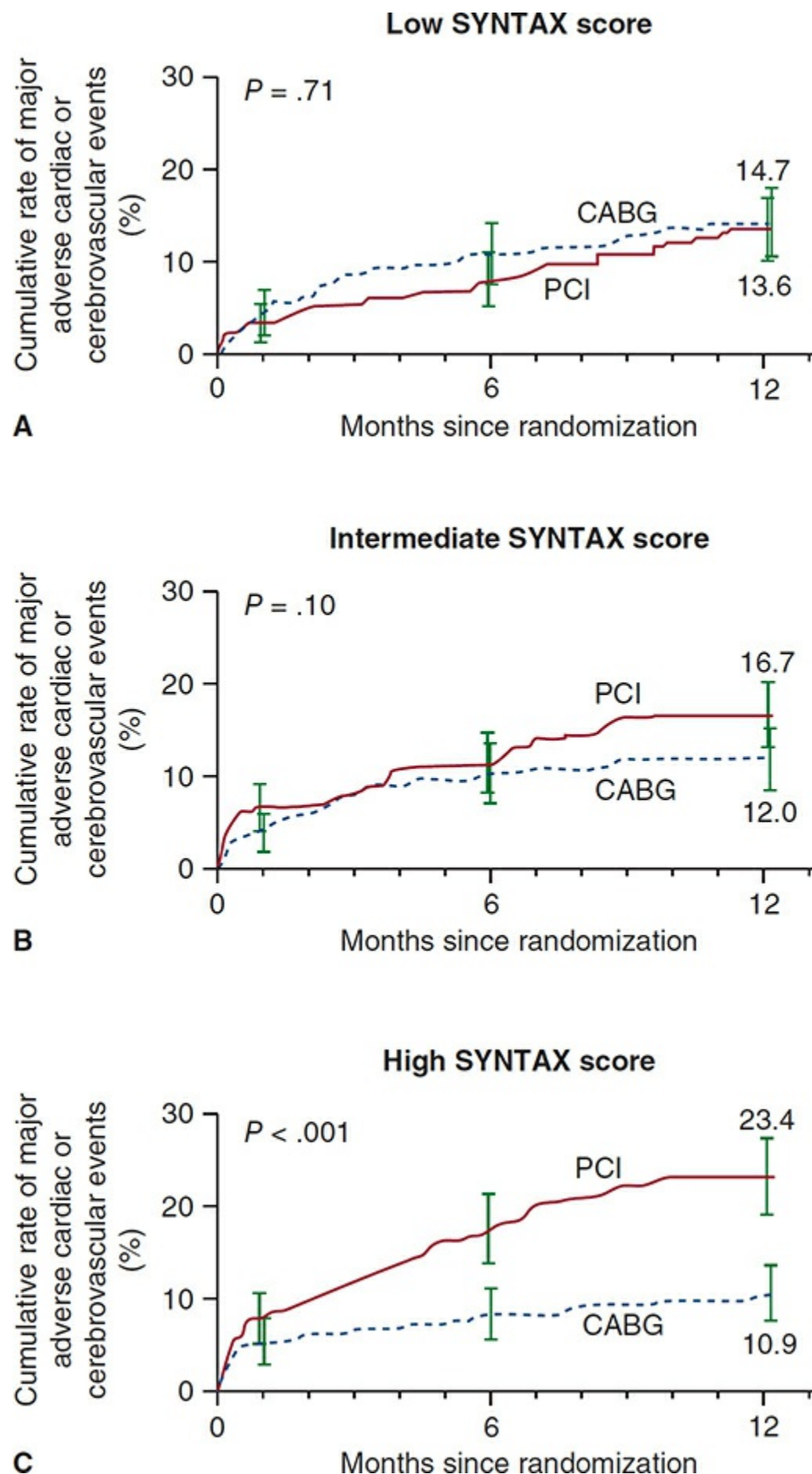


FIGURE 43-1 SYNTAX score and benefit of revascularization strategy. The rates of major adverse cardiac or cerebrovascular events 12 months following therapy are reported for patients with low (A), intermediate (B), or high (C) SYNTAX score. The bars indicate 1.5 standard errors. Note the improved outcomes among patients with high SYNTAX scores who underwent revascularization. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. (Reproduced with permission from Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease, *N Engl J Med*. 2009 Mar 5;360(10):961-972.)

43-6. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 43*) The SYNTAX score can support decision making about the optimal strategy for revascularization of left main stenosis. Angiographic features that contribute to the score include options A through D, as well as: total occlusion (number of segments involved, age of total occlusion, presence of a blunt stump, presence of bridging collateral, antegrade versus retrograde filling of the first segment beyond the occlusion, side branch involvement); bifurcation lesion: angulation between the distal main vessel and the side branch $< 70^\circ$; the presence of an aorto-ostial atherosclerotic lesion; the presence of severe vessel tortuosity at the lesion site; atherosclerotic lesion length > 20 mm; the presence of heavily calcified plaque; the presence of thrombus; and the presence of diffuse or small-vessel disease.

43-7. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 43*) Coronary artery calcification observed on cardiac CT correlates positively with the presence of established atherosclerosis (option A). The coronary artery calcification score is a quantitative measure of overall vascular calcium burden (option B). The presence of calcium in the vessel wall does not correlate with the degree of luminal obstruction (option C), although the overall burden may predict future coronary heart disease events (option D). Serial coronary artery calcification scoring to assess the rate of disease progression is not recommended (option E).

- 43-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 43*) Options A through D represent important, core components of optimal management programs for secondary prevention in those with established CAD. In addition, psychosocial counseling, physical activity, and exercise training are important and beneficial components.
- 43-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 43*) Patients infected with the HIV appear to be at increased risk for a wide range of inflammatory vascular diseases, including CAD. This may occur as a manifestation of HIV itself; low CD4⁺ T-cell count has been associated with the presence of coronary artery stenotic lesions > 50% of the luminal diameter. Alternatively, CAD in HIV-infected persons could occur as a result of HAART use (option A). Compared to HIV-negative patients, the prevalence of noncalcified coronary plaques is approximately threefold higher in HIV-positive patients on HAART therapy (option B), which may account for parallel findings in similar patients suggesting that the risk of incident MI is increased approximately fourfold (option C). The mechanistic link between HAART and CAD remains speculative, but it may involve cross-reactivity between protease inhibitors and lipid metabolism-regulating proteins that results in dyslipidemia, insulin resistance, central adiposity, and lipodystrophy (option D). In selected HIV patients at elevated risk for cardiovascular disease, protease inhibitors may be inappropriate; under these circumstances, consultation with an infectious disease specialist to determine optimal HIV therapy is advised, as is the early institution of aggressive risk factor control (eg, statin therapy).
- 43-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 43*) Many observational studies have demonstrated a positive, continuous, and graded relationship between systemic blood pressure and cardiovascular disease risk. In patients with stable ischemic heart disease, hypertension is a risk factor for recurrent MI (option A), an observation that is likely a consequence of the associated endothelial dysfunction and the adverse effects of persistently elevated afterload on myocardial function and oxygen demand. In patients with diabetes, uncontrolled hypertension is a strong predictor of premature death, cardiovascular morbidity, and progressive nephropathy (option B). The Systolic Blood Pressure Intervention Trial (SPRINT) tested whether the conventional systolic blood pressure (SBP) goal of 140 mm Hg is sufficient to reduce cardiovascular events in nondiabetic, nonstroke patients at increased cardiovascular risk. Compared to a standard treatment goal SBP < 140 mm Hg, patients randomized to intensive therapy (SBP < 120 mm Hg) had lower risk for the composite end point of MI, other ACSs, stroke, HF, and death from cardiovascular causes at 1 year (HR, 0.75; 95% CI, 0.64–0.89; *P* < .001; option C). Directionally similar findings were observed for all-cause mortality, although the beneficial effects of intensive therapy were associated with an attendant increase in the number of medications prescribed, systemic hypotension, syncope, electrolyte abnormalities, and acute kidney injury. Studies have affirmed the benefit of treating hypertension in the elderly, although debate continues about the optimal targets and thresholds (option D). Blood pressure control is an important preventive strategy for incident heart failure (option E).

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CHAPTER 44

Coronary Artery Bypass Grafting and Percutaneous Interventions in Stable Ischemic Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

44-1. Which of the following findings on noninvasive testing should prompt referral of a patient for coronary angiography?

- A. Exercise treadmill, > 2 mm of ST depression
- B. Failure to increase systolic pressure to > 120 mm Hg or a sustained decrease of > 10 mm Hg during exercise
- C. Resting perfusion abnormalities > 10% of the myocardium
- D. Stress-induced left ventricular dilatation
- E. All of the above

Questions 44-2, 44-3, and 44-4 relate to the following vignette:

A 55-year-old man with hypertension, dyslipidemia, and type II diabetes mellitus treated with subcutaneous insulin undergoes coronary angiography following a high-risk stress test with hypotensive blood pressure response. He is found to have proximal left anterior descending coronary artery (LAD) stenosis of 85%, as well as a 70% lesion in the mid-right coronary artery.

44-2. Which of the factors in this patient's history would favor referral for surgical revascularization?

- A. A history of diabetes
- B. The presence of two or more preexisting risk factors
- C. Young age
- D. SYNTAX score of 20
- E. None of the above

44-3. In this patient, what benefits would be expected from surgical revascularization with coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI)?

- A. Reduction in the composite end point of death, nonfatal myocardial infarction, and nonfatal stroke
- B. Reduced all-cause mortality risk compared to PCI at 5 years
- C. Reduction in the need for repeat revascularization
- D. All of the above
- E. None of the above

44-4. If this patient were to undergo surgical revascularization, which of the following would be true about the risk of stroke?

- A. CABG and PCI are associated with similar risks of stroke
- B. Higher stroke risk in patients undergoing CABG is evident only at 1 year follow-up
- C. Previous stroke is a risk factor for CABG-related stroke in this population
- D. Chronic renal failure is not related to long-term stroke risk in this population
- E. The risk of stroke over longitudinal follow-up is fivefold higher in patients undergoing CABG compared with PCI in this population

Questions 44-5 and 44-6 relate to the following vignette:

A 76-year-old man with angina is found to have multivessel coronary artery disease (MV CAD) involving his proximal left anterior descending coronary artery (95%) as well as in an obtuse marginal branch from the left circumflex coronary artery (80%), and distal right coronary artery (75%). An echocardiogram demonstrates no valvular disease, but the left ventricular ejection fraction is 30%.

44-5. Which strategy represents the optimal approach to this patient's management?

- A. Optimal medical therapy
- B. CABG
- C. Multivessel PCI
- D. Durable left ventricular device consideration
- E. Noninvasive ischemia testing to guide revascularization decisions

44-6. What is the optimal modality of viability testing to inform the decision to undertake surgical revascularization in this patient?

- A. Single-photon emission computed tomography (SPECT)
- B. Dobutamine stress echocardiography (DSE)
- C. Thallium scan
- D. Evidence of Q-waves on ECG
- E. There is no certain, evidence-based role for viability testing in this setting

Questions 44-7, 44-8, and 44-9 relate to the following vignette:

A 55-year-old man without diabetes presents with typical angina symptoms and no prior history of coronary artery disease. Noninvasive stress testing is positive, and he is referred for coronary angiography, which demonstrates an 80% proximal LAD stenosis as well as a 90% mid-vessel stenosis in a dominant right coronary artery.

44-7. If there is uncertainty as to the hemodynamic significance of this patient's coronary stenoses, which of the following can be undertaken during the catheterization procedure to support a role for revascularization:

- A. Fractional flow reserve (FFR) measurement
- B. Optical coherence tomography (OCT)
- C. Intravascular ultrasound (IVUS)
- D. Noninvasive FFR by coronary CT
- E. None of the above

44-8. In reviewing this patient's coronary angiogram, which of the following are important elements to ascertain when assessing the anatomic complexity of underlying coronary artery disease?

- A. Number of lesions
- B. Bifurcation types and angulation
- C. Aorto-ostial lesions
- D. Severe tortuosity
- E. All of the above

44-9. Which of the following statements is true regarding a hybrid approach (percutaneous coronary intervention and surgical revascularization) to revascularization?

- A. A hybrid approach is used commonly in all patients without diabetes mellitus where center of expertise is present
- B. Insufficient data exist to strongly recommend hybrid revascularization
- C. Hybrid approach is strongly preferred in this patient
- D. PCI would be preferred in this patient
- E. None of the above

44-10. In patients with ischemia identified on noninvasive stress testing, which of the following is true?

- A. The role of PCI in the absence of uncontrolled symptoms is uncertain in such patients
- B. PCI should be undertaken in all patients with documented ischemia and anatomically amenable disease
- C. Optimal medical therapy (OMT) is usually ineffective at controlling angina symptoms
- D. PCI is associated with improved mortality in patients with stable coronary artery disease
- E. None of the above

ANSWERS

44-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 44*) Patients referred for diagnostic noninvasive stress testing should be considered for coronary angiography in the presence of high-risk findings. A number of such factors are suggested ([Table 44-1](#); options A through D are incorrect).

TABLE 44-1 Criteria for Referring Patients to Coronary Angiography

Exercise Treadmill Exercise treadmill, > 2 mm of ST depression; Exercise-induced ST-segment elevation; Exercise-induced ventricular tachycardia/ventricular fibrillation; and Failure to increase systolic pressure to > 120 mm Hg or a sustained decrease of > 10 mm Hg during exercise
Myocardial Perfusion Imaging Severe left ventricular dysfunction, not readily explained; Resting perfusion abnormalities > 10% of the myocardium; Severe stress-induced left ventricular dysfunction; Stress-induced perfusion abnormalities involving > 10% of the myocardium or stress and mental scores indicating multiple territories at risk; Stress-induced left ventricular dilatation; and Increased lung uptake.
Stress Echocardiography Inducible wall motion abnormalities involving > 2 segments or 2 coronary beds
Coronary Computed Tomography Multivessel obstructive coronary disease or left main stenosis

Modified with permission from Mancini GB, Gosselin G, Chow B, et al. Canadian Cardiovascular Society. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease, *Can J Cardiol*. 2014 Aug;30(8):837-849.

- 44-2. The answer is A.** (*Hurst’s The Heart, 14th Edition, Chap. 44*) Patients with diabetes mellitus have consistently been found to have more favorable outcomes with surgical revascularization than with percutaneous revascularization ([Figure 44-1](#)).¹ This is true even among contemporary trials employing the use of drug-eluting stents. Other clinical variables (options B through E) in this patient would not have an obvious influence on preference for one modality of revascularization over another.
- 44-3. The answer is D.** (*Hurst’s The Heart, 14th Edition, Chap. 44*) The FREEDOM trial was designed to address the optimal coronary revascularization strategy in patients with diabetes and multivessel CAD in the absence of left main disease, prior CABG, prior stenting within 6 months, and current ST-segment elevation myocardial infarction.² In FREEDOM, the overall 5-year Kaplan-Meier estimates of the primary composite end point of death, nonfatal myocardial infarction, and nonfatal stroke indicated a 26.6% event rate in the first-generation DES group compared to 18.7% in the CABG group ($P < .005$; option A alone is incorrect). Indeed, in FREEDOM, CABG was associated with a significantly reduced all-cause mortality risk compared to PCI at 5 years, and the mortality curves continued to diverge in favor of CABG throughout follow-up (option B alone is incorrect). The results of FREEDOM and subsequent meta-analyses lead to a Class I recommendation in the 2014 ACC/AHA guidelines stating that CABG was associated with improved survival in diabetics with multivessel CAD. This was upgraded from a Class II recommendation in 2012. CABG remains the revascularization treatment of choice for diabetic patients with multivessel disease. This is particularly true if a left internal mammary artery (LIMA) graft to the left anterior descending artery was performed. In general, the need for repeat revascularization is reduced with coronary artery bypass surgery versus PCI (option C alone is incorrect).

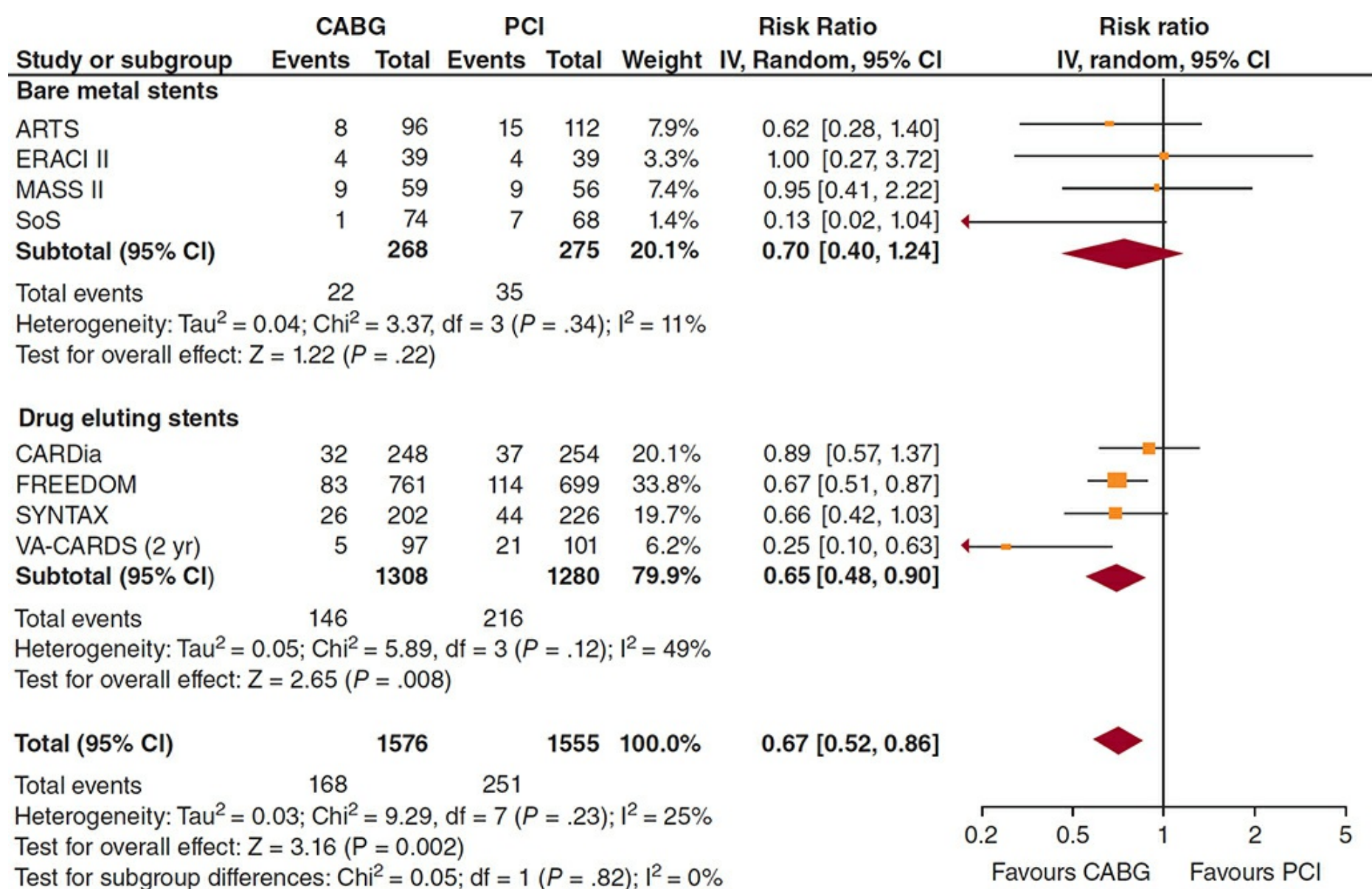


FIGURE 44-1 Forest plots for individual studies and pooled risk ratios for all-cause mortality in randomized controlled trials comparing patients with diabetes and multivessel coronary artery disease who underwent coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) after 5 years or the longest follow-up. CI, confidence interval. (Reproduced with permission from Verma S, Farkouh ME, Yanagawa B, et al. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials, *Lancet Diabetes Endocrinol* 2013 Dec;1(4):317-328.)

- 44-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 44*) For patients with diabetes undergoing CABG in the FREEDOM trial, there was an excess of early stroke compared to PCI (option A is incorrect). The difference accrued mostly over the first 30 days after follow-up (option B is incorrect). In an analysis from the FREEDOM CABG cohort, predictors of early stroke included a prior history of stroke, the use of warfarin, and whether CABG was performed outside North America. In long-term follow-up, the strongest predictor of stroke was the presence of chronic renal insufficiency (option D is incorrect). Over 5 years of follow-up, CABG was still associated with a significantly higher stroke rate compared to PCI (5.2% vs 2.4%; $P = .03$; option E is incorrect).
- 44-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 44*) In the Surgical Treatment for Ischemic Heart Failure (STICH) study, patients with ischemic cardiomyopathy and an ejection fraction of 35% or less were randomly assigned to CABG versus OMT alone and followed for 9.8 years.³ Although there was no significant difference between OMT alone and OMT plus CABG with respect to the primary end point (death from any cause), there were more cardiovascular deaths in the OMT group (297 deaths, 49.3%) compared to the CABG group (247 deaths, 40.5%; hazard ratio, 0.79; 95% CI, 0.66–0.93; $P = .006$; option A is incorrect). A 2009 meta-analysis has suggested that CABG is the preferred mode of revascularization in patients with left ventricular dysfunction (option C is incorrect),⁴ although this analysis was largely limited to patients in the bare metal stent era. The patient does not currently have indications for durable LVAD consideration (option D is incorrect). Noninvasive, ischemia-guided revascularization decisions in patients with left ventricular systolic dysfunction have not been shown to improve outcomes (option E is incorrect).
- 44-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 44*) In a substudy of the STICH trial, among the 1212 patients enrolled in the overall randomized trial, 601 underwent viability assessment with SPECT or DSE.⁵ Of these 601, 298 were randomly assigned to receive OMT plus CABG and 303 to receive OMT alone. There was no significant mortality interaction between viability status and treatment assignment ($P = 0.53$), suggesting that viability assessment did not identify patients with a differential survival benefit from CABG + OMT versus OMT alone. In all patients, while there was an unadjusted association between the presence of viable myocardium and mortality, this was no longer significant after adjusting for potential confounders. Thus, the role of viability testing across modalities (options A through D) remains uncertain in this population.
- 44-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 44*) The fractional flow reserve (FFR) is a lesion-specific index of stenosis severity defined as the ratio of maximum flow in the presence of stenosis to normal maximum flow. In practice, FFR is estimated as the ratio of coronary artery pressure distal to a lesion of interest to aortic pressure, averaged

over the entire cardiac cycle, with variation in microvascular resistance minimized by pharmacologic induction of maximal hyperemia. FFR is useful to reclassify the functional severity of angiographically indeterminate coronary lesions and to define the utility of PCI. Evidence to date suggests that when a lesion is functionally significant, as defined by an $\text{FFR} \leq 0.80$, revascularization may be beneficial. For example, in the FAME study, which randomized 1005 patients with multivessel CAD to PCI guided by angiography alone or angiography plus FFR, a strategy of FFR guidance was associated with a reduced rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year (13.2% vs 18.3%; $P = .02$) as well as a reduced usage of stents per patient (1.9 ± 1.3 vs 2.7 ± 1.2 ; $P < .001$).⁶ In the FAME 2 trial, which randomized 888 patients with at least one functionally significant stenosis to PCI plus medical therapy or medical therapy alone, PCI conferred a significant reduction in death, nonfatal myocardial infarction, and urgent revascularization at 2 years.⁷ Figure 44-2 depicts the overall decision making regarding revascularization in patients with stable ischemic heart disease, including the role of FFR.

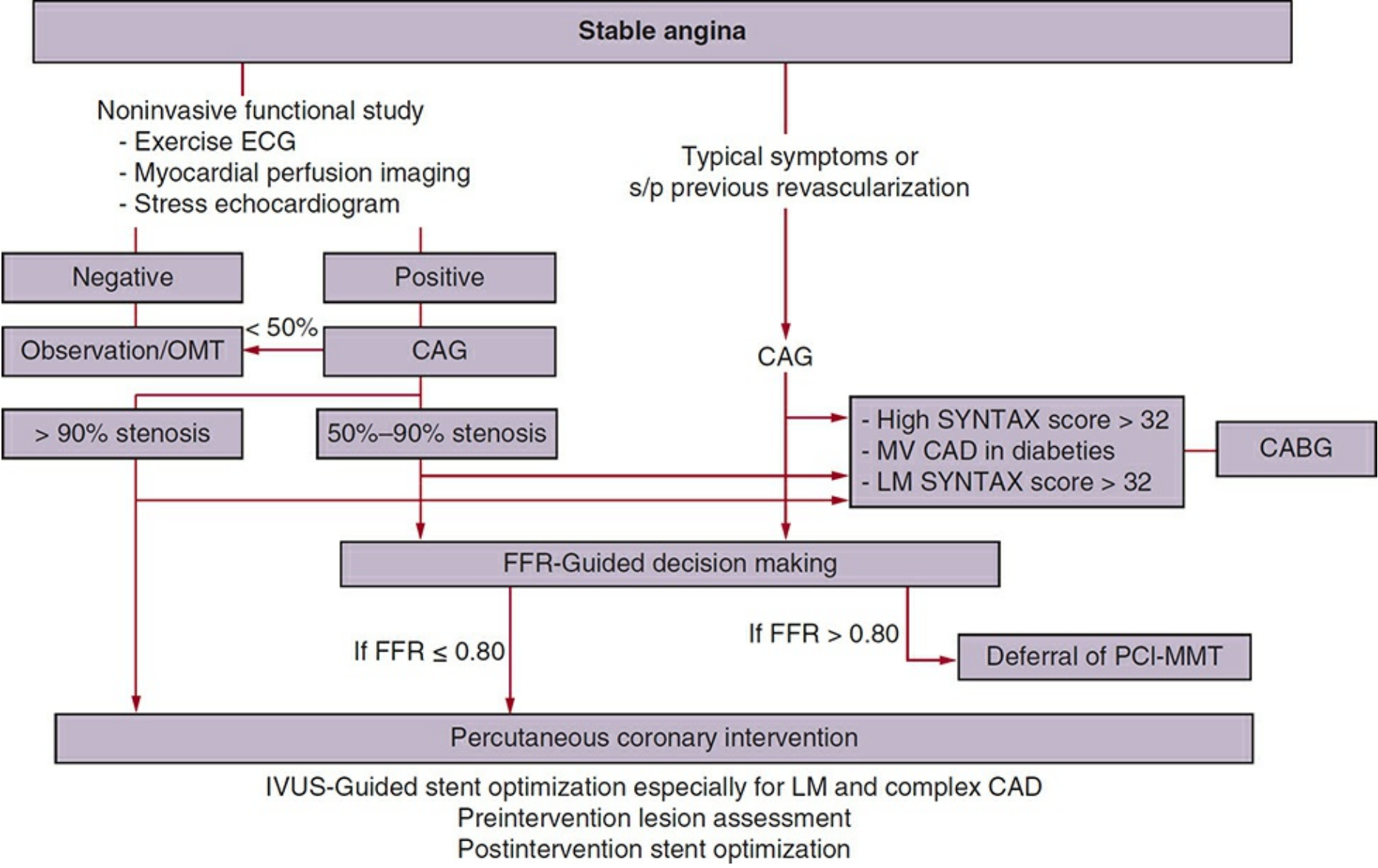


FIGURE 44-2 Proposed algorithm for assignment to revascularization in stable ischemic heart disease. CABG, coronary artery bypass grafting; CAG, coronary angiography; ECG, electrocardiogram; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LM, left main; OMT, optimal medical therapy; MV CAD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

44-8. The answer is E. (*Hurst’s The Heart, 14th Edition, Chap. 44*) The extent and complexity of CAD are important parameters informing triage to percutaneous coronary intervention (PCI) versus CABG in patients with stable multivessel CAD. The SYNTAX Score (SS), developed for use in the multicenter Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial provides a semiquantitative angiographic measure of disease complexity that is useful for this purpose. For a given patient, the SS represents a sum of scores for every lesion with > 50% diameter stenosis in vessels with a diameter > 1.5 mm. Elements of this score are listed in Table 44-2 (including options A through D; option E is correct).

TABLE 44-2 The SYNTAX Score Algorithm

1. Dominance
2. Number of lesions
3. Segments involved per lesion, with lesion characteristics
4. Total occlusions with subtotal occlusions:
a. Number of segments
b. Age of total occlusions
c. Blunt stumps
d. Bridging collaterals
e. First segment beyond occlusion visible by antegrade or retrograde filling
f. Side branch involvement
5. Trifurcation, number of segments diseased

6. Bifurcation type and angulation
7. Aorto-ostial lesion
8. Severe tortuosity
9. Lesion length
10. Heavy calcification
11. Thrombus
12. Diffuse disease, with number of segments

Adapted with permission from Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease, *EuroIntervention*. 2005 Aug;1(2):219-227.

- 44-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 44*) The use of a hybrid approach to coronary revascularization is gaining popularity and may be an appropriate alternative for a carefully selected subset of patients with limited CAD involving the proximal or mid LAD and at least one other non-LAD coronary artery. In hybrid coronary revascularization (HCR), a minimally invasive surgical approach is used to bypass the LAD with a LIMA graft in combination with stenting of non-LAD targets. This is believed to leverage the advantages of surgical arterial revascularization of the LAD and substitution of advanced stent technology for saphenous vein grafts for the other targets. HCR is offered in about one third of hospitals in the United States but represents less than 1% of CABG procedures (option A is incorrect). The current body of evidence is limited to observational studies and a small pilot randomized trial (option B is correct). The current ACC/AHA guidelines on coronary revascularization consider HCR only when PCI of the LAD is considered suboptimal, and therefore, it is given a Class IIa recommendation (option C is incorrect).
- 44-10. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 44*) Percutaneous coronary intervention is largely reserved for two major groups of patients, namely those who have inadequate symptom relief or persistent reduction in quality of life despite OMT and those with noninvasive testing indicating risk for ischemic events. Currently, the National Heart, Lung, and Blood Institute is sponsoring the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial to evaluate the benefit of PCI in patients with high-risk features on noninvasive testing compared to OMT alone. In a prior pivotal randomized trial (COURAGE), 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease were randomized to undergo PCI with OMT or OMT alone. The primary outcome (death from any cause and nonfatal myocardial infarction during a follow-up period of median 4.6 years) did not differ during the two groups at follow-up (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87–1.27; $P = 0.62$). Similarly, there were no significant differences in the composite of death, myocardial infarction, and stroke ($P = 0.62$); hospitalization for acute coronary syndrome ($P = 0.56$); or myocardial infarction ($P = 0.33$). The ISCHEMIA trial will critically inform this ongoing question in the contemporary treatment era, but at the present time the role of routine PCI in the absence of symptoms refractory to OMT is uncertain.

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CHAPTER 45

Rehabilitation of the Patient with Coronary Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

45-1. Which of the following is *not* a benefit of cardiac rehabilitation (CR)?

- A. Improved heart rate recovery
- B. Decreased levels of high-density lipoprotein (HDL) cholesterol
- C. Dose-dependent reduction in mortality
- D. Improved left ventricular (LV) function
- E. Decreased depression symptoms

45-2. A 54-year-old man recovering from a cardiovascular event is referred to you for medical evaluation prior to initiating CR. Which of the following is a contraindication to enrollment in a CR program?

- A. Hypertension
- B. Coronary artery bypass graft (CABG) surgery
- C. Myocardial infarction (MI)
- D. Unstable angina
- E. All of the above

45-3. A 59-year-old man with long-standing hypertension is admitted to the ER with a myocardial infarction (MI). Following revascularization with coronary stenting, he improves clinically. Which of the following signs suggests that the patient is ready for a gradual mobilization program and CR?

- A. No signs of decompensated heart failure
- B. New or recurrent chest pain in the past hour
- C. Steadily increasing troponin levels
- D. A recent change in cardiac rhythm
- E. None of the above

45-4. During a treadmill exercise stress test, a 60-year-old male patient becomes tired and asks to stop the test. Which of the following signs and symptoms is *not* considered an absolute test termination criterion?

- A. Cyanosis
- B. Dyspnea
- C. Ataxia
- D. Severe chest pain
- E. Dizziness

45-5. Following medical evaluation, a 60-year-old male patient is determined to be in the class C risk category for exercise training. Which of the following statements about his exercise capacity is *true*?

- A. His exercise capacity is approximately 10 METs
- B. His oxygen uptake during exercise is < 21 mL O₂ uptake/kg/min
- C. His maximum HR during exercise (HR_{max}) is 140 beats per minute
- D. He is unlikely to develop angina at a workload < 6 METs
- E. None of the above

45-6. A 65-year-old woman with stable angina is evaluated for an exercise training program. Which of the following is a *correct* method for determining appropriate exercise intensity?

- A. Exercise intensity is determined by the patient's oxygen consumption at rest

- B. Exercise intensity is equal to the maximum heart rate achieved during the exercise test
- C. Exercise intensity is estimated as the heart rate equal to 220 minus the age in years
- D. Exercise intensity is extrapolated from a plot of the heart rate versus oxygen consumption
- E. All of the above

45-7. Which of the following is *not* a physiologic effect of smoking on the cardiovascular system?

- A. Cell migration to the intima
- B. Increased fibrinogen levels
- C. Decreased platelet adhesion to the endothelium
- D. Smooth muscle proliferation
- E. None of the above

45-8. A 57-year-old hypertensive male patient is evaluated following myocardial infarction. Which of the following findings would suggest that this patient has secondary hypertension?

- A. Uncontrolled hypertension despite three medications
- B. Nocturnal dipping of blood pressure on 24-hour ambulatory monitoring
- C. Minimal alcohol consumption
- D. Low salt sensitivity
- E. All of the above

45-9. Following a psychological evaluation of a 48-year-old woman recovering from a myocardial infarction, you observe that she feels anxious about her cardiovascular health and upcoming CR. Which of the following is *not* a physiologic response to anxiety?

- A. Platelet and macrophage cell activation
- B. Increased levels of blood lipids
- C. Increased heart rate
- D. Decreased myocardial oxygen demand
- E. Increased blood pressure

45-10. Which of the following is the most common reason for the underutilization of CR programs?

- A. Lack of physician referral
- B. Higher socioeconomic status
- C. Patient age < 65 years old
- D. Male gender
- E. None of the above

ANSWERS

45-1. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 45*) Clinical trials have demonstrated many clinical benefits of exercise-based CR.¹ A number of mechanistic effects seem to contribute to this clinical benefit. For example, exercise has anti-inflammatory effects by *increasing* HDL cholesterol levels (option B). Heart rate recovery is an indicator of cardiovascular (CV) health, and impaired heart rate recovery predicts mortality. In a study of patients with abnormal heart rate recovery prior to starting CR, the exercise program resulted in a 41% improvement in heart rate recovery (option A).² Following MI, exercise training has proven benefits on LV function and remodeling (option D), and the effects were greatest when the exercise training was started 1 week after MI and lasted longer than 12 weeks.³ It has been estimated that 20% to 45% of patients demonstrate depression following MI.⁴ Improved fitness was associated with decreased depressive symptoms and decreased mortality (option E).⁵ Furthermore, the relationship between the number of CR sessions completed in older patients and improved outcomes found a dose-dependent reduction in mortality and recurrent MI (option C).

45-2. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 45*) To establish a safe and effective program of comprehensive CV disease risk reduction and rehabilitation, each patient should undergo a careful medical evaluation and exercise test before participating in an outpatient CR/SP program. CR was initially implemented to reduce hospitalizations after MI (option C), but given the benefits for CV health, the concept was expanded to include patients with several conditions. This includes patients undergoing cardiac surgery and coronary interventions (option B), and those with a high cardiovascular risk, namely hypertensives (option A). Nevertheless, there are absolute contraindications to CR, including all conditions where physical exercise carries a significant risk of adverse effect, such as unstable angina (option D). The indications and contraindications for CR are summarized in [Table 45-1](#).

TABLE 45-1 Clinical Indications and Contraindications for Inpatient and Outpatient Cardiac Rehabilitation.

Indications
<ul style="list-style-type: none">• Medically stable after myocardial infarction• Stable angina• Coronary artery bypass graft surgery• Percutaneous transluminal coronary angioplasty or other transcatheter procedure• Compensated congestive heart failure• Cardiomyopathy• Heart or other organ transplantation• Other cardiac surgery including valvular and pacemaker insertion (including implantable cardioverter defibrillator)• Peripheral arterial-vascular disease• High-risk cardiovascular disease ineligible for surgical intervention• Sudden cardiac death syndrome• End-stage renal disease• At risk for coronary artery disease, with diagnosis of diabetes mellitus, hyperlipidemia, hypertension, etc.• Other patients who may benefit from structured exercise and/or patient education (based on physician referral and consensus of the rehabilitation team)
Contraindications
<ul style="list-style-type: none">• Unstable angina• Resting systolic blood pressure > 200 mm Hg or diastolic > 110 mm Hg• Orthostatic blood pressure decrease of > 20 mm Hg with symptoms• Critical aortic stenosis (peak systolic pressure gradient of > 50 mm Hg with an aortic valve orifice area of < 0.75 cm² in an average-size adult)• Acute systemic illness or fever• Uncontrolled atrial or ventricular arrhythmias• Uncontrolled sinus tachycardia (> 120 bpm)• Uncompensated congestive heart failure• Third-degree heart block (without pacemaker)• Active pericarditis or myocarditis• Recent embolism• Thrombophlebitis• Resting ST-segment displacement (> 2 mm)• Uncontrolled diabetes (resting blood glucose > 300 mg/dL [17 mmol/L] or > 250 mg/dL [14 mmol/L]) with ketones present• Orthopedic problems prohibiting exercise• Other metabolic conditions such as acute thyroiditis, hypokalemia or hyperkalemia, hypovolemia, etc.

- 45-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 45*) Phase I of CR traditionally begins in the hospital and lasts for the duration of hospitalization. This phase emphasizes a gradual, progressive approach to exercise and an education program that helps the patient understand the disease process, the rehabilitation process, and initial preventive efforts to slow the progression of disease. Simple breathing and leg exercises are commenced with a program of gradual mobilization. The emphasis at this stage is to counteract the negative effects of deconditioning after a cardiac event. A patient is considered appropriate for daily ambulation/mobilization if he or she meets four criteria: there is no new or recurrent chest pain during the previous 8 hours (option B), neither troponin nor creatine phosphokinase (CPK) is increasing (option C), there are no signs of decompensated heart failure (option A), and there is no significant change in ECG or rhythm in the previous 8 hours (option D).
- 45-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 45*) Exercise stress testing in CR is performed to measure the ischemic threshold, assess for arrhythmias, assess exercise tolerance, evaluate hemodynamic response (blood pressure, heart rate), and observe for signs and symptoms of ischemia. The test is traditionally carried out using a treadmill or a cycle ergometer with monitoring of ECG, heart rate, and blood pressure. The RPE Scale and the individual's description of his or her levels of angina and dyspnea (option B) are also assessed. The exercise test usually lasts for 8 to 12 minutes and is terminated when the patient develops symptoms, such as chest pain (option D), or when he or she achieves a physiologic end point, such as 85% of maximal predicted heart rate. The subject's general appearance during the exercise test is also of value and should be carefully observed during the exercise test. Signs of poor perfusion, such as cyanosis (option A) or pallor, and increasing nervous system symptoms, such as ataxia (option C), dizziness (option E), and vertigo, serve as absolute test termination criteria.
- 45-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 45*) The exercise goals of a CR program are developed based on an individual's baseline ability and limitations. Risk stratification is performed with each patient before the initiation of an exercise program. The guidelines published by the AHA use four categories (A, B, C, and D) according to clinical characteristics. Class C individuals are at moderate or high risk of cardiac complications during exercise due to one of the following: a history of multiple MIs or cardiac arrest, New York Heart Association class III or IV angina, exercise capacity of less than 6 METs (option A), and significant angina or ischemia at a workload < 6 METs (option D). One

MET is defined as 3.5 mL O₂ uptake/kg/min, therefore this patient has an oxygen uptake capacity of < 21 mL O₂ uptake/kg/min during exercise (option B). His maximum HR can be estimated as 220 minus his age in years, therefore his HR_{max} is equal to 160 beats per minute (option C).

- 45-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 45*) The intensity for exercise training can be calculated from the exercise test (option A), and for cardiac patients, the heart rate is the most common method used. There are three methods of using the heart rate, and these include the direct method, the percentage of HR_{max}, and the heart rate reserve.⁶ In the direct method, the heart rate is plotted against oxygen consumption, and the appropriate exercise intensity is extrapolated (option D). The percentage of HR_{max} method uses 65% to 75% of the heart rate achieved during the exercise test, which approximates from 40% to 60% of an individual's maximal oxygen consumption (VO₂ max) (option B). In the heart rate reserve method, the resting heart rate is subtracted from the maximal heart rate (estimated as 220 minus the age in years) to give the heart rate reserve. If an exercise prescription of 60% to 80% of maximal oxygen consumption is required, then 60% and 80% values of the heart rate reserve are calculated, and the resting heart rate is added to each value to give the training heart rate values (option C).
- 45-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 45*) Cigarette smoking, a major risk factor for the development of CHD, remains a leading cause of preventable death worldwide. The causal relationship between smoking and CV disease is well established. The effects of smoking on the CV system include stimulation of smooth muscle proliferation (option D) and cell migration to intima (option A), increase in platelet adhesion to the endothelium (option C), and an increase in fibrinogen levels (increased clotting) (option B). Smoking cessation will reduce the subsequent risk of mortality by up to 9%.⁷ Observational studies in post-MI patients suggest that this may be reflected as a halving of long-term mortality.⁸
- 45-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 45*) Evidence exists regarding the importance of hypertension as a risk factor for CV disease and the importance of lifestyle measures and appropriate medication to treat and control hypertension. Ambulatory blood pressure monitoring can confirm the diagnosis of hypertension. A change in lifestyle behaviors may have important effects on BP control. Excessive alcohol consumption (option C) is associated with hypertension, and reduction or cessation of alcohol consumption has been shown to improve blood pressure and to reduce need for medication. Most people with hypertension are salt-sensitive (option D), and reductions in dietary salt are effective. There is a direct link between increasing body weight and blood pressure levels, particularly if fat distribution is central. Stress has a major effect on blood pressure, and recognizing and eliminating this factor may have important effects. Secondary causes of hypertension may be diagnosed if one of the following is noted: blood pressure of ≥ 180/110 mm Hg, uncontrolled hypertension despite three medications (option A), or nondipping of blood pressure during 24-hour ambulatory blood pressure monitoring (option B).
- 45-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 45*) Psychosocial factors may affect the occurrence and recurrence of CHD and may affect rehabilitation. Anxiety and depression are prevalent in both cardiac patients and their families and are associated with increased morbidity and mortality. Although they may be normal responses after a cardiac event and a natural part of recovery after any life-threatening or stressful event, in excess, they may seriously impede rehabilitation. Anxiety can affect both short- and long-term recovery after a cardiac event. It may relate more to how an individual responds to his or her condition than to its severity. Anxiety may trigger a variety of physiologic responses such as increased levels of circulating lipids (option B), platelet and macrophage cell activation (option A), and increased heart rate (option C), blood pressure (option E), and myocardial oxygen demand (option D), all of which have have implications for the development of atherosclerosis, ischemia, MI, and sudden death.
- 45-10. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 45*) The most common barrier to CR is a lack of physician referral (option A). Despite national guidelines in the United States designating CR as a Class IA recommendation, Menezes et al.⁹ report that up to 80% are not referred. In particular, women (option D), those of lower socioeconomic status (option B), and patients over age 65 (option C) have lower rates of referral.¹⁰ The EuroAspire survey analyzed records and interviews of 9000 patients and reported that only one-third of patients with CHD received any form of CR.¹¹ Even among those referred to CR, the dropout rate is high among post-MI patients. Importantly, once referred to CR, the reasons for nonattendance were more likely due to personal factors, such as perceptions of heart disease and family influence, versus physical issues.

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SECTION 8

Valvular Heart Disease

CHAPTER 46

Acute Rheumatic Fever

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 46-1.** Acute rheumatic fever (ARF) is a multisystem autoimmune response to untreated or partially treated group A *Streptococcus* (GAS) pharyngitis. Which of the following statements about ARF is *false*?
- A. First attacks are rare in the very young
 - B. The peak incidence of ARF occurs in those age 5 to 15 years
 - C. ARF is rare in adults older than age 35
 - D. ARF is equally common in males and females
 - E. No association with ethnic origin has been found
- 46-2.** The incidence of ARF began to decline in developed countries toward the end of the 19th century, and by the second half of the 20th century, ARF had become rare in most affluent populations. Which of the following factors contributed *least* to this decline?
- A. More hygienic living conditions
 - B. Less crowded living conditions
 - C. Better nutrition
 - D. Improved access to medical care
 - E. The advent of antibiotics
- 46-3.** A 31-year-old man with a prior history of rheumatism in every joint at the age of 15 presented to the emergency department complaining of pain in the left hip and right knee. His physical examination revealed a systolic murmur, loudest at the apex and radiating to the axilla. Which of the following statements about the antibodies that contribute to this rheumatic valvulitis is *false*?
- A. They target the N-acetyl- β -D-glucosamine–dominant epitope of the GAS carbohydrate
 - B. They recognize sequences in α -helical proteins (eg, myosin and tropomyosin)
 - C. They are neutralized by appropriate antibiotic therapy
 - D. Their serum levels fall significantly after surgical removal of inflamed valves
 - E. None of the above
- 46-4.** A 29-year-old healthy woman with a past medical history of ARF as a child is seen in the clinic because her 12-year-old daughter has recently been diagnosed with ARF. She is concerned that ARF may be running in her family and that her 2-year-old son may thus be at increased risk of having ARF. Which of the following genetic factors has been associated with the development of ARF?
- A. Human leukocyte antigen (HLA) Class II alleles
 - B. Polymorphisms of transforming growth factor- β 1
 - C. Immunoglobulin genes
 - D. Certain B-cell alloantigens
 - E. All of the above
- 46-5.** The long-term clinical consequence of ARF is related to permanent cardiac damage. Which of the following patients is most likely to have permanent cardiac damage from ARF?
- A. 15-year-old boy with pleuritic chest pain and diffuse concave-shaped ST-elevation on ECG
 - B. 25-year-old man with acute heart failure with an EF of 25% and recurrent tachyarrhythmias
 - C. 27-year-old man with joint pain and a pansystolic murmur loudest at the apex and radiating to the axilla
 - D. 19-year-old woman with central pleuritic chest pain, positive troponins, and raised inflammatory markers

E. All of the above

46-6. ARF usually has an acute febrile onset and presents with variable combinations of major and minor manifestations. In which of the following presentations is the evidence of a preceding GAS infection *not* needed to diagnose ARF?

- A. 12-year-old girl with involuntary, purposeless, rapid, and abrupt movements associated with muscular weakness and emotional lability
- B. 13-year-old boy with polyarthritis, temperature of 38.5°C, and ESR of 60 mm in the first hour
- C. 9-year-old girl with polyarthritis, temperature of 39.5°C, and ESR of 120 mm in the first hour
- D. 12-year-old boy with pleuritic chest pain, arthralgia, fever, and ESR of 72 mm in the first hour
- E. None of the above

46-7. A 10-year-old girl was brought by her mother to the emergency department complaining of personality changes, with inappropriate behavior, restlessness, and outbursts of anger or crying. During the physical examination, the patient was asked to squeeze the examiner's hand. This resulted in repetitive irregular squeezes. Which of the following statements about the patient's condition is *false*?

- A. It must be associated with other manifestations of ARF in order to confirm the diagnosis
- B. It may be the sole expression of the ARF
- C. It is a neurologic disorder
- D. It occurs in up to 30% of cases of ARF
- E. The abnormal movements disappear during sleep

46-8. An 11-year-old girl was brought to the emergency department by her parents complaining of pains in the right hip and left knee. On physical examination, there was a pink rash on the patient's trunk. She had a temperature of 39.5°C, and the ESR was 120 mm in the first hour. Which of the following statements about this rash is *false*?

- A. It is itchy and evanescent in nature
- B. It affects the trunk predominantly
- C. It may be fleeting and disappear within hours
- D. It may be brought out by a warm bath or shower
- E. It is found in only 4% to 15% of cases

46-9. A 12-year-old boy was brought by his parents to the emergency department complaining of a rash over the bony surfaces of his elbows, wrists, and knees. Three to 4 weeks ago, the patient presented to the same hospital with pleuritic chest pain, arthralgia, fever, and ESR of 72 mm in the first hour. The physical examination revealed some nodules over the bony surfaces of his elbows, wrists, and knees. Which of the following statements about these nodules is *false*?

- A. They generally appear later in the course of the disease after several weeks of illness
- B. They are seen most commonly in patients with carditis
- C. They are firm and painful
- D. The overlying skin is not usually inflamed
- E. They occur in less than 10% of cases of ARF

46-10. There is no definitive laboratory test for ARF, with the diagnosis based on a combination of clinical manifestations and laboratory evidence of previous streptococcal infection. Which of the following laboratory findings *cannot* be used as evidence of a preceding strep infection?

- A. Increased or rising antistreptolysin O titer
- B. Increased or rising of other streptococcal antibodies
- C. A positive throat swab culture
- D. Rapid antigen test for group A β -hemolytic streptococci
- E. None of the above

ANSWERS

46-1. The answer is C. (*Hurst's The Heart, 14th Edition, Chap. 46*) Acute rheumatic fever is equally common in males and females, but RHD is more common in females in almost all populations.^{1,2} First attacks are rare in the very young (option A); only 5% of first episodes arise in children younger than age 5, and the disease is almost unheard of in those younger than age 2 (option A). The peak incidence of ARF occurs in those age 5 to 15 (option B), with a decline thereafter such that cases are rare in adults older than age 35 (option C).³ No association with sex or ethnic origin has been found (options D and E).

- 46-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 46*) This decline is attributed to more hygienic and less crowded living conditions, better nutrition, improved access to medical care, and, to a lesser extent, the advent of antibiotics in the 1950s. The decline in the prevalence of RHD in wealthy countries has followed a similar pattern, albeit with a delay compared to ARF incidence, which is explained by the chronic nature of RHD.
- 46-3. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 46*) The antibodies that contribute to rheumatic valvulitis target the N-acetyl- β -D-glucosamine–dominant epitope of the GAS carbohydrate,⁴ but they also recognize sequences in α -helical proteins (eg, myosin and tropomyosin).⁵ These antibodies are elevated in patients with valvular involvement in ARF, significantly reduce after the surgical removal of inflamed valves, and correlate with poor prognosis.⁶ At this stage, antibiotics are ineffective and do not reduce the level of circulating antibodies.
- 46-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 46*) Host factors have been considered to be important ever since familial clustering was reported last century. Associations between disease and HLA Class II alleles have been identified, but the alleles associated with susceptibility or protection differ depending on the population investigated.⁷ High concentrations of circulating mannose-binding lectin and polymorphisms of transforming growth factor- β 1 and immunoglobulin genes also are associated with ARF.⁸⁻¹⁰ Certain B-cell alloantigens are expressed to a greater level in patients with ARF or RHD than controls, with family members having intermediate expression, suggesting that these antigens are markers of inherited susceptibility.
- 46-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 46*) Although rheumatic carditis involves the pericardium, myocardium, and endocardium, fibrinous pericarditis (options A and D) and interstitial myocardial involvement (options B and D) typically resolve without residual damage, whereas verrucous valvulitis (option C) is usually associated with lasting damage. Notably, the pathologic changes also indicate that, unlike in the more common lymphocytic form of myocarditis, heart muscle cells are spared in rheumatic carditis.¹¹
- 46-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 46*) The diagnosis of ARF is made when the patient develops two major manifestations, or one major manifestation and at least two minor manifestations; in addition, evidence of a preceding infection with GAS must be demonstrated using streptococcal serology. The exceptions are patients who present with chorea (option A) or indolent carditis because these manifestations may only become apparent months after the inciting streptococcal infection, so additional manifestations may not be present and streptococcal serology testing may be normal.¹²
- 46-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 46*) Mild chorea may best be demonstrated by asking the patient to squeeze the examiner's hand. This results in repetitive irregular squeezes labeled as the milking sign. Emotional lability manifests in personality changes, with inappropriate behavior, restlessness, and outbursts of anger or crying.¹³ Sydenham chorea may be associated with other manifestations of ARF but may also be the sole expression of the disease (options A and B). It is a neurologic disorder characterized by involuntary, purposeless, rapid, and abrupt movements associated with muscular weakness and emotional lability (option C). Chorea occurs in up to 30% of cases of ARF (option D). The abnormal movements disappear during sleep (option E).
- 46-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 46*) Erythema marginatum is a nonitchy (option A), evanescent rash that is pink or slightly red and that affects the trunk predominantly (option B). The rash extends centrifugally, and the skin in the center returns toward normal. The rash may be fleeting and may disappear within hours (option C). It may be brought out by a warm bath or shower (option D). It is reported to be found in only 4% to 15% of cases and may be difficult to detect in dark-skinned patients (option E).
- 46-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 46*) These nodules generally appear later in the course of the disease after several weeks of illness and are seen most commonly in patients with carditis. They are firm and painless; the overlying skin is not inflamed and may vary in size from a few millimeters to several centimeters. They are most commonly located over bony surfaces or tendons such as elbows, wrists, knees, occiput, and spinous processes of the vertebrae. These occur in less than 10% of cases of ARF.
- 46-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 46*) Evidence of preceding streptococcal infection may be demonstrated by increased or rising antistreptolysin O titer, other streptococcal antibodies, a positive throat swab culture, or a rapid antigen test for group A β -hemolytic streptococci.

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CHAPTER 47

Aortic Valve Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 47-1.** A 65-year-old man was referred for cardiac consultation following a 2-year history of dyspnea on minimal exertion. He had a coronary angiography in the past that revealed normal coronaries. His physical examination revealed a 3/6 systolic ejection systolic murmur across the precordium. An echo was obtained showing left ventricular dysfunction with an EF of 38%, a calcified aortic valve with a mean gradient of 29 mm Hg, and AVA (aortic valve area) of 0.9 cm². Which of the following is the best next step in the management of this patient?
- A. SAVR after coronary angiography
 - B. Left and right cardiac catheterization
 - C. Exercise treadmill testing
 - D. TAVR
 - E. Dobutamine stress echocardiography (DSE)
- 47-2.** A 67-year-old man with a prior medical history of hypertension and atrial fibrillation was referred for cardiac consultation following a 2-year history of chest discomfort on minimal exertion. His physical examination revealed a late peaking 3/6 ejection systolic murmur with a soft and single S2. An echo was obtained showing left ventricular hypertrophy with an EF of 62%, moderate right ventricular dysfunction, moderate mitral regurgitation, a calcified aortic valve with a mean gradient of 29 mm Hg, and AVA of 0.7 cm². Which of the following parameters may *not* be a contributor to paradoxical low-flow, low-gradient severe aortic stenosis?
- A. Hypertensive heart disease
 - B. Atrial fibrillation
 - C. Right ventricular dysfunction
 - D. Occult aortic regurgitation
 - E. Mitral regurgitation
- 47-3.** A 52-year-old man with no prior medical history was referred for cardiac consultation following a 1-year history of chest pain and dyspnea on exertion. Palpation of the carotid arteries demonstrated a pulse low in volume and delayed in upstroke. His remaining physical examination revealed a late-peaking 3/6 systolic ejection murmur with a soft and single S2. An echo was obtained showing left ventricular hypertrophy with an EF of 62%, a calcified bicuspid aortic valve with a mean gradient of 44 mm Hg, and AVA of 0.7 cm². Which of the following is the best next step in the management of this patient?
- A. SAVR after coronary angiography
 - B. Stress cardiac magnetic resonance
 - C. Exercise treadmill testing
 - D. TAVR
 - E. DSE
- 47-4.** A 65-year-old man was referred for cardiac consultation following a 2-year history of dyspnea on exertion. He had a coronary angiography in the past that revealed normal coronaries. Palpation of the carotid arteries demonstrated a pulse low in volume and delayed in upstroke. His remaining physical examination revealed a late-peaking 3/6 systolic ejection murmur with a soft and single S2. An echo was obtained showing left ventricular hypertrophy with an EF of 64%, a calcified aortic valve with a mean gradient of 28 mm Hg, and AVA of 1.5 cm². Which of the following is the best management approach for this patient?
- A. SAVR after coronary angiography
 - B. Left and right cardiac catheterization
 - C. Exercise treadmill testing
 - D. TAVR

E. Observe

47-5. An 89-year-old woman with a prior history of CABG, hypertension, type 2 diabetes, stage III CKD, COPD, and peripheral artery disease presented to the clinic for routine follow-up. The patient appeared frail but denied any cardiovascular symptoms. Her physical examination revealed parvus tardus carotid pulse and a late-peaking 3/6 systolic ejection murmur with a single S2. An echo was obtained showing left ventricular dysfunction with an EF of 44%, a calcified aortic valve with a mean gradient of 48 mm Hg, and AVA of 0.8 cm². Which of the following is the best management approach for this patient?

- A. SAVR after coronary angiography
- B. Left and right cardiac catheterization
- C. Exercise treadmill testing
- D. TAVR
- E. Observe

47-6. A 29-year-old man with no known cardiovascular history presented to the emergency department complaining of acute dyspnea. On arrival, the patient appeared pale with cool distal extremities, peripheral cyanosis, and tachycardia. The physical examination revealed a relatively unsustained left ventricular impulse that was neither hyperdynamic nor significantly displaced to the left, a short and soft diastolic murmur, pulmonary rales, and an elevated JVP. A wide pulse pressure was *not* seen during the examination. An echo was obtained showing a premature mitral valve closure and fluttering of the mitral valve leaflets, most effectively demonstrated using M-mode echocardiography. Continuous-wave Doppler of the regurgitant jet demonstrated a markedly shortened pressure half-time. Which of the following is the best next step in the management of this patient?

- A. Aortic balloon counterpulsation
- B. Beta-blocker infusion
- C. Atrial pacing
- D. SAVR
- E. TAVR

47-7. Holodiastolic reversal of flow within the descending aorta detected by pulsed-wave Doppler is an abnormal finding typically consistent with at least moderate (present in the proximal descending aorta) or severe (present in the abdominal aorta) AR. In which of the following scenarios can holodiastolic retrograde aortic flow *not* be seen in the absence of AR?

- A. Ruptured sinus of Valsalva aneurysm
- B. Left-to-right shunt across a patent ductus arteriosus
- C. Upper extremity arterio-venous fistula
- D. Aortic dissection with diastolic flow into the false lumen
- E. None of the above

47-8. A 66-year-old woman with a prior history of type 2 diabetes, depression, and childhood asthma was referred by her GP to the cardiology clinic because of a 2-year history of progressive dyspnea on exertion. Physical examination revealed a holodiastolic murmur best heard along the left sternal border and a 2/4 diastolic rumble noted at the apex. In addition, there was a sharp carotid upstroke followed by a rapid decline. An echocardiogram was obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 52%, and left ventricular end systolic dimension of 49 mm. Which of the following is the best next step in the management of this patient?

- A. Nitroprusside infusion
- B. Initiation of an angiotensin-converting enzyme inhibitor
- C. Angiotensin-converting enzyme inhibitor and follow-up
- D. TAVR
- E. SAVR

47-9. A 71-year-old man with a prior history of diet-controlled type 2 diabetes and COPD was referred by his GP to the cardiology clinic because of a heart murmur. He was a very active gentleman without any cardiovascular symptoms. Physical examination revealed a diastolic blowing sound best heard along the left sternal border with the patient sitting up and leaning forward and an exaggerated carotid upstroke. In addition, the apical beat was easily visible and palpable, and it was oriented downward and to the left. An echocardiogram was obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 65%, and left ventricular end systolic dimension of 67 mm. Which of the following is the best next step in the management of this patient?

- A. Initiation of nifedipine
- B. Exercise treadmill testing
- C. SAVR
- D. Exercise echocardiography
- E. Follow-up

47-10. A 61-year-old man with no known cardiovascular history was referred by his GP to the cardiology clinic because of a

heart murmur. He was active and asymptomatic. Physical examination revealed a holodiastolic murmur best heard along the left sternal border. In addition, there was a sharp carotid upstroke followed by a rapid decline. An echocardiogram was obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 45%, and left ventricular end systolic dimension of 37 mm. Which of the following is the best next step in the management of this patient?

- A. Initiation of a vasodilator
- B. Exercise treadmill testing
- C. Follow-up
- D. Exercise echocardiography
- E. SAVR

ANSWERS

- 47-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 47*) There is a discrepancy between gradient and valve area calculation, and this needs to be sorted out before making any decision with regard to the interventions (options A and D are thus not correct). This patient may have low-flow/low-gradient severe AS with reduced EF. AS severity may be difficult to assess under resting conditions in low LVEF patients,¹⁻⁵ and DSE (option E) can help clarify the issue by allowing reassessment of the AVA at a higher flow. With normalized flow, a patient with true severe AS increases the mean transaortic gradient in tandem with valve flow so that AVA remains nearly constant. A patient with pseudo-severe AS, a condition where low flow causes an overestimation of AS severity, increases valve flow with little increase in gradient, resulting in increased AVA. Options B and C would not be useful in resolving the discrepancy between gradient and valve area calculation in this case.
- 47-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 47*) Multiple explanations for low forward flow in the setting of normal EF have been proposed.⁶⁻⁸ It is generally held that this group has small LV volumes (concentric remodeling), so a normal EF of a small end-diastolic volume produces a small stroke volume and hence a low gradient. Hypertension (option A) has been shown to reduce the transaortic gradients in experimental models and patients, primarily because of changes in transvalvular flow rates and not directly as a result of changes in arterial compliance.^{6,7} Right ventricular dysfunction (option C), atrial fibrillation (option B), and mitral regurgitation (option E) are independently associated with low-flow, low-gradient AS.⁸ Aortic regurgitation (option D) is associated with higher transaortic flow rates and, consequently, should not cause low-flow, low-gradient AS. Option D is therefore the correct answer.
- 47-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 47*) All evidence (clinical, physical exam findings, aortic gradient, and AVA) points to severe symptomatic AS in a patient with high-flow and normal EF, so SAVR is indicated (option A). No further tests are needed (options B, C, and E). SAVR remains the standard of care in low-risk patients, especially in individuals with a congenital bicuspid aortic valve. (Insufficient data are currently available for the routine use of TAVR (option D) in bicuspid aortic valve patients.)
- 47-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 47*) There are discrepancies between clinical, physical exam, and echocardiographic findings; and this needs to be sorted out before making any decision with regard to the interventions (options A and D are thus not correct). Invasive hemodynamic measurement is the best next step for such situations when there is discordance in clinical presentation and noninvasive data regarding AS severity (option B). In such cases direct measurement of aortic valve gradient (g) and cardiac output (CO) is indicated. These data are entered into the Gorlin equation: $AVA = CO/44.3\sqrt{g}$, where cardiac output is expressed as flow per systole. Careful attention must be paid to proper pressure and cardiac output measurement.⁹ Options C and E would be inappropriate for these reasons.
- 47-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 47*) In the truly asymptomatic AS patient, the risk of sudden death is small, probably less than 1% per year.^{10,11} However, AVR is recommended for very rare asymptomatic patients who have developed LV dysfunction and for the patient with severe AS undergoing another cardiac operation where it would be unwise to fail to correct severe AS during surgery.^{12,13} Because this is a high-risk patient (elderly, frail, multiple comorbidities and history of a prior CABG), TAVR (instead of SAVR) would be the best option in this case (options A and D). This patient has some indications for AVR, and therefore options B, C, and E would be inappropriate.
- 47-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 47*) This is a case of acute AR. Vasodilator therapy with sodium nitroprusside may stabilize the patient during transport to the operating department. Aortic balloon counterpulsation (option A) is contraindicated because it worsens AR. Beta-blockers (option B) should be avoided in acute AR because they prolong diastole and may worsen AR. Atrial pacing (option C) to increase heart rate might be of theoretical benefit¹⁴; however, this does not have an established role in clinical practice. Several studies have demonstrated that emergency aortic valve replacement (SAVR, and thus option D) can be performed with low operative mortality and good long-term results in acute AR. The data with TAVR are currently lacking (option E).

- 47-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 47*) In the absence of AR, holodiastolic retrograde aortic flow can be seen most commonly in hypertensive patients with reduced aortic compliance¹⁵ but also in other conditions such as a left-to-right shunt across a patent ductus arteriosus (option B), upper extremity arterio-venous fistula (option C), a ruptured sinus of Valsalva (option A), or aortic dissection with diastolic flow into the false lumen (option D). It is thus important to assess diastolic flow reversal in the context of these possible confounders. The correct answer is therefore option E.
- 47-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 47*) As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease, and symptom onset is a clear indication of surgical intervention (options A, B, and C are thus not correct).¹⁶ In most cases, SAVR is standard therapy (option E). Because TAVR (option D) relies on native valve calcification to hold the TAVR in place, TAVR is not widely used in treating AR, although newer valve designs may overcome this problem. The correct answer is therefore option E.
- 47-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 47*) As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease, and symptom onset is a clear indication of surgical intervention.¹⁶ However, some patients develop LV dysfunction without having or noticing symptom onset. To avoid persistent postoperative LV dysfunction, AVR should occur before the LV end-diastolic dimension increases from 50 to 55 mm (option C is thus the correct answer).^{17,18} Although adding stress imaging is of uncertain value (option D), if exercise imaging is performed, attention should be focused on LV ejection fraction at exercise. However the utility of imaging LV function during exercise remains controversial (option D). Because afterload is often excessive in AR, there have been attempts to lower afterload using ACE inhibitors, direct vasodilators, or dihydropyridine calcium channel blockers (option A) in the hope of forestalling the need for AVR. These efforts have met with confusing and contradictory results, such that no clear recommendation can be made about their usage.¹⁹⁻²¹ Options B and E are not correct for the reasons explained above.
- 47-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 47*) As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease, and symptom onset is a clear indication of surgical intervention.¹⁶ However, some patients develop LV dysfunction without having or noticing symptom onset. To avoid persistent postoperative LV dysfunction, AVR should occur before EF declines to 50% to 55% (option E is thus the correct answer) or before LV end-diastolic dimension increases from 50 to 55 mm.^{17,18} Although adding stress imaging is of uncertain value (option D), if exercise imaging is performed, attention should be focused on LV ejection fraction at exercise. However, the utility of imaging LV function during exercise remains controversial (option B and D). Because afterload is often excessive in AR, there have been attempts to lower afterload using ACE inhibitors, direct vasodilators (option A), or dihydropyridine calcium channel blockers in the hope of forestalling the need for AVR. These efforts have met with confusing and contradictory results, such that no clear recommendation can be made about their usage.¹⁹⁻²¹ Options B and C are not correct for the reasons explained above.

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CHAPTER 48

Degenerative Mitral Valve Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 48-1.** A 45-year-old woman with a prior history of diet-controlled type 2 diabetes and chronic obstructive pulmonary disease (COPD) was referred by her GP to the cardiology clinic because of a heart murmur. She was very active and without any cardiovascular symptoms. Physical examination revealed a soft late-systolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating mild prolapse and leaflet thickening with normal coaptation. Left ventricular function and dimensions are normal (ejection fraction 65%). Which of the following is the best next step in the management of this patient?
- A. Vasodilator therapy
 - B. Beta-blocker therapy
 - C. Elective mitral valve repair
 - D. Elective mitral valve replacement
 - E. Observe with echocardiographic annual follow-up
- 48-2.** Mortality after mitral valve repair in patients with degenerative disease correlates with age, with an average risk of 1% for patients below 65 years, 2% for those aged 65 to 80 years, and 4% for octogenarians. Which of the following is *not* an independent predictor of postoperative survival?
- A. Severe symptoms (NYHA class III or IV)
 - B. LV dysfunction
 - C. A regurgitant orifice area $\geq 40 \text{ mm}^2$
 - D. A large color Doppler jet appearance
 - E. The presence of long-standing atrial fibrillation
- 48-3.** A 55-year-old woman with no prior cardiac history was referred by her GP to the cardiology clinic because of a heart murmur. She admitted to living a sedentary lifestyle, and she denied overt cardiovascular symptoms. Physical examination revealed a mid-to-late systolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained, clearly demonstrating moderate to severe mitral valve prolapse and regurgitation without flail segments. Left ventricular function and dimensions were normal (ejection fraction 62%). Which of the following is the best next step in the management of this patient?
- A. Exercise Doppler echocardiography
 - B. Cardiac CT
 - C. Cardiac magnetic resonance
 - D. Nuclear perfusion scan
 - E. Cardiac catheterization
- 48-4.** A 69-year-old man with a prior history of type 2 diabetes and dyslipidemia was referred by his GP to the cardiology clinic because of a heart murmur. He was a very active person without any cardiovascular symptoms. Physical examination revealed a holosystolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating severe prolapse with loss of coaptation, LVEF of 63%, and LVESD of 38 mm. According to the ACC/AHA guidelines, which of the following statements does *not* justify prompt correction of MR in general?
- A. Severe MR is not a benign condition
 - B. Surgical correction in patients with severe MR is unavoidable
 - C. Patients with severe MR may or may not develop symptoms
 - D. Mitral valve prolapse is almost always a repairable disease in reference centers
 - E. The risk of operative mortality in mitral valve repair surgery is, on average, only 10%

- 48-5.** A 59-year-old woman with a prior history of depression and childhood asthma was referred by her GP to the cardiology clinic because of a new onset atrial fibrillation. During the visit, the patient denied any cardiovascular symptoms. Physical examination revealed a holosystolic murmur best heard at the apex and radiating to the axilla. The ECG showed atrial fibrillation with a controlled ventricular response. An echocardiogram was obtained demonstrating severe mitral valve prolapse with loss of coaptation, LVEF of 66%, and LVESD of 36 mm. Which of the following is the best next step in the management of this patient?
- Vasodilator therapy
 - Exercise Doppler echocardiography
 - Elective mitral valve repair
 - Elective mitral valve replacement
 - Observe with echocardiographic annual follow-up
- 48-6.** Tricuspid regurgitation does *not* always regress after correction of left-sided valve disease, and reoperations for residual or recurrent tricuspid regurgitation are associated with a higher mortality risk even in experienced centers (up to 15%). Which of the following factors may be used as a guide in deciding on concomitant tricuspid valve repair in patients undergoing mitral valve repair?
- Degree of TR
 - Annular dimensions
 - Leaflet coaptation or mismatch between leaflet and annulus
 - Presence of atrial fibrillation
 - All of the above
- 48-7.** A 71-year-old woman with a prior history of type 2 diabetes, COPD, and dyslipidemia was referred by her GP to the cardiology clinic because of a heart murmur. She reported otherwise feeling fit and well. Physical examination revealed a holosystolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating severe mitral valve prolapse with loss of coaptation, LVEF of 62%, LVESD of 38 mm, and SPAP of 62 mm Hg. Which of the following is the best next step in the management of this patient?
- Beta-blocker therapy
 - Exercise Doppler echocardiography
 - Elective mitral valve repair
 - Elective mitral valve replacement
 - Observe with echocardiographic annual follow-up
- 48-8.** Severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem, with the only definitive solution being mechanical (ie, mitral valve repair or replacement). Which of the following factors may be a reason to favor mitral valve replacement over repair?
- Lower perioperative risk
 - Improved preservation of left ventricular function
 - Improved event-free survival in the majority of patients
 - Greater freedom from prosthetic valve-related complications
 - Greater certitude to correct complex lesions with extensive distortion of multiple scallops
- 48-9.** A 58-year-old man with a history of mitral valve prolapse and mild mitral regurgitation, was referred by his GP to the cardiology clinic because of a 6-month history of exertional dyspnea. Physical examination revealed a pansystolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating severe prolapse with a coaptation gap, LVEF of 62%, and LVESD of 38 mm. Which of the following is the best next step in the management of this patient?
- Immediate admission for management of acute severe MR
 - Exercise Doppler echocardiography
 - Elective mitral valve repair
 - Elective mitral valve replacement
 - Observe with echocardiographic annual follow-up
- 48-10.** An ejection fraction $\leq 60\%$ or a left ventricular end-systolic dimension ≥ 40 mm, though useful at indicating the onset of LV dysfunction, are imprecise and reflect changes in the LV after the negative impact of MR has already been realized. Which of the following new markers indicating an adverse myocardial response to MR has the potential to determine the optimum timing of surgery in the very near future?
- High brain natriuretic peptide (BNP) levels
 - A lower percentage of age- or sex-predicted metabolic equivalents
 - Lower heart rate recovery after exercise
 - Left atrial dimensions
 - All of the above

ANSWERS

- 48-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 48*) Currently there is no indication to intervene (options C and D) in less than severe primary mitral regurgitation, except in symptomatic patients where there is a high suspicion that MR grade may be underestimated. The use of beta-blockers (option B) or vasodilators (option A) to treat mitral valve prolapse in normotensive subjects is not recommended. The correct answer is therefore to observe with echocardiographic annual follow-up (option E).
- 48-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 48*) Some of the identified independent predictors of postoperative survival include severe symptoms (NYHA class III or IV—option A is thus true and therefore incorrect), LV dysfunction ($EF < 60\%$ or $LVEDD > 40\text{ mm}$ —option B is thus incorrect), a regurgitant orifice area $\geq 40\text{ mm}^2$ (option C is thus incorrect), left atrial dimensions (left atrial index $\geq 60\text{ mL/m}^2$ or $LA > 55\text{ mm}$), or the presence of pulmonary hypertension or long-standing atrial fibrillation (option E is thus incorrect). The size of the color Doppler jet is subject to many technical parameters, and it is not reliably predictive of outcomes after repair. The correct answer is therefore D.
- 48-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 48*) Again, currently there is no indication to intervene in less than severe mitral regurgitation, except in symptomatic patients where there is a high suspicion that MR grade may be underestimated. In such patients, exercise testing is useful to clarify the decision making (option A is thus the correct answer).¹ In fact, exercise Doppler echocardiography can be used in asymptomatic patients with moderate to severe primary MR with preserved LV ejection fraction for immediate risk stratification and to guide the timing of mitral valve surgery, especially for those in whom the risk-to-benefit ratio of surgical intervention is uncertain or borderline.² Computed tomography (option B), cardiac magnetic resonance (option C), and nuclear perfusion scan (option D) techniques have been compared to echocardiography for MR assessment, but they are not routinely recommended unless there are critical considerations about chamber remodeling or viability.^{3,4} Although TEE is more accurate than TTE in locating the site and severity of structural abnormalities and quantifying the severity of MR, TEE during an initial diagnostic evaluation is only indicated in patients with inconclusive or technically difficult TTE examinations. Once the mainstay of evaluation, invasive hemodynamic evaluation (option E) is now reserved for cases in which the diagnosis of the severity and impact of mitral regurgitation is uncertain.
- 48-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 48*) Prompt correction of asymptomatic mitral regurgitation with preserved left ventricular function (class IIa), in other words before the development of traditional triggers, is based on several axioms: (1) severe MR is not a benign condition (option A is thus incorrect),⁵ and if left uncorrected it carries a significant rate of excess mortality associated with increased rates of heart failure and atrial fibrillation⁶; (2) surgical correction in patients with severe MR is unavoidable (option B is thus incorrect); (3) patients with severe MR or ventricular dysfunction may or may not develop classical symptoms (option C is thus incorrect); and (4) mitral valve prolapse is a repairable disease in reference centers (option D is thus incorrect) with excellent operative outcomes (mortality and stroke rates $< 1\%$; not 10% as stated in option E, which is therefore the correct answer) and durability.⁷⁻⁹
- 48-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 48*) According to the 2014 ACC/AHA new classification of the severity of valve lesions, this patient is at stage C1 of degenerative mitral valve disease, and the presence of the new onset of atrial fibrillation¹² is considered a class IIa trigger for mitral surgery in asymptomatic patients with preserved left ventricular function (options B and E are not the best next step in the management of this patient, who needs her valve to be fixed).¹³ Severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem with only a mechanical solution (option A is thus not correct); at this time the only definitive treatment is mitral valve repair (option C is thus the correct answer). All prolapsing valves are repairable, and mitral valve replacement should not be an option if appropriate referral patterns are followed (option D is thus not correct).¹⁴
- 48-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 48*) The final decision should be guided not only by the degree of regurgitation (\geq moderate) (option A is thus incorrect) but also by annular dimensions ($\geq 40\text{ mm}$ when measured by echocardiography in the apical 4-chamber view) (option B is also thus incorrect); leaflet coaptation or mismatch between leaflet and annulus on direct inspection (option C is thus incorrect); and the presence of atrial fibrillation (option D is thus incorrect), pulmonary hypertension, right ventricular dysfunction, and/or left ventricular dysfunction. The correct answer is therefore option E.
- 48-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 48*) According to the 2014 ACC/AHA new classification of the severity of valve lesions, this patient is at stage C1 of degenerative mitral valve disease, and the presence of pulmonary hypertension¹² is also considered a class IIa trigger for mitral surgery in asymptomatic patients with preserved left ventricular function (options B and E are not the best next step in the management of this patient, who needs her valve to be fixed).¹³ Again, severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem (option A is thus not correct) with only a mechanical solution; at this time the only definitive treatment is mitral valve repair (option C is thus the correct answer). All prolapsing valves are repairable, and mitral valve replacement should not be an option if appropriate referral patterns are followed (option D is thus not correct).¹⁴

- 48-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 48*) Mitral valve repair is favored over replacement for several reasons, including a lower perioperative risk (option A is thus not correct), improved preservation of left ventricular function (option B is thus not correct), improved event-free survival in most patients (option C is thus not correct), and greater freedom from prosthetic valve–related complications (option D is thus not correct) such as thromboembolism, anticoagulant-related hemorrhage, and endocarditis.^{15-17,19} However, in a minority of cases, anatomical factors pertaining to the extent of valvular disruption (eg, perforation) and operator-related factors pertaining to local experience and expertise make replacement more appropriate than repair (option E is thus the correct answer).
- 48-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 48*) This patient is symptomatic but stable and therefore does not require immediate admission for the management of acute severe MR (option A). The standard class I indications for mitral valve surgery are the onset of symptoms or of left ventricular dysfunction.^{19,20} Although guidelines currently contemplate mitral valve replacement (option D) as an acceptable option, mitral valve repair is the preferred option in patients with mitral valve prolapse (option C is therefore the correct answer).¹⁴ Options B and E are not the best next step in the management of this patient, who needs her valve to be fixed.
- 48-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 48*) In this context, new potential triggers for surgical intervention in asymptomatic patients might include high BNP levels (option A is thus correct),²¹ a lower percentage of age- or sex-predicted metabolic equivalents (option B is thus correct), or lower heart rate recovery after exercise (option C is thus correct),¹ the left ventricular ejection index,^{22,23} and left atrial dimensions (option D is thus correct).^{24,25} The correct answer is therefore option E.

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CHAPTER 49

Ischemic Mitral Regurgitation

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 49-1.** A 61-year-old man with a prior history of diet-controlled type 2 diabetes, ischemic heart disease, and COPD was referred for cardiology consultation for a heart murmur. He was a very active man without any cardiovascular symptoms. His physical examination revealed a 2/6 holosystolic murmur loudest at the apex. An echo was obtained showing normal valve leaflets, chords, and annulus; small central MR jet area of 15% LA on Doppler; and mildly dilated LV size with fixed regional wall motion abnormalities. According to the ACC/AHA stages for ischemic MR (IMR), at which of the following stages would this patient be?
- A. Stage A
 - B. Stage B
 - C. Stage C1
 - D. Stage C2
 - E. Stage D
- 49-2.** IMR is an independent predictor of cardiovascular mortality and HF following MI. Which of the following statements about IMR is *false*?
- A. The magnitude of risk is proportional to the severity of MR
 - B. The estimated 1-year mortality for patients with severe IMR ranges from 15% to 40%
 - C. For patients with moderate IMR undergoing coronary artery bypass surgery, concomitant mitral valve replacement should always be performed
 - D. Adverse outcomes are associated with a smaller calculated effective regurgitant orifice (ERO) in IMR when compared to primary MR
 - E. None of the above
- 49-3.** The MitraClip is a transcatheter mitral device for use in high-risk or inoperable patients with severe MR and suitable anatomic criteria. Which of the following characteristics is *not* part of the desirable anatomic criteria for percutaneous edge-to-edge repair of MR using this type of device?
- A. Coaptation length ≥ 2 mm
 - B. Short posterior leaflet
 - C. Flail width < 15 mm
 - D. MV orifice area > 4 cm²
 - E. MV leaflet length > 1 cm
- 49-4.** IMR is a dynamic lesion, and MR severity can vary over time and during exercise. Which of the following statements about IMR during exercise is *false*?
- A. The severity of IMR at rest predictably determines the severity of IMR during exercise
 - B. Exercise-induced increase in IMR provides additional prognostic information over resting evaluation
 - C. Exercise echocardiography may be used to further evaluate patients with exertional dyspnea out of proportion to the degree of resting IMR
 - D. An increase in EROA of ≥ 13 mm² during exercise is associated with increased mortality
 - E. An increase in EROA of ≥ 13 mm² during exercise is associated with increased HF hospitalizations
- 49-5.** A 68-year-old man with a prior history of myocardial infarction with PCI to the LAD was referred for cardiology consultation for decreased exercise tolerance. His physical examination revealed a displaced apex beat downward and to the left and a holosystolic murmur loudest at the apex and radiating to the axilla. An echo was obtained showing regional wall motion abnormalities with reduced LV systolic function, LV dilation with severe tethering of mitral leaflets, and a large

wall-impinging jet pattern with an estimated regurgitant volume of 40 mL. Defining severe MR requires the careful integration of multiple echocardiographic parameters. Which of the following echo findings is *not* an indicator of severe MR?

- A. Peak mitral valve E-wave velocity < 1.2 m/s
- B. A dense triangular continuous-wave Doppler profile
- C. Systolic flow reversal in the pulmonary veins
- D. Vena contracta width ≥ 0.7 cm
- E. MR regurgitant jet area/left atrial area ratio $\geq 40\%$

49-6. A 75-year-old woman with a prior history of ischemic heart failure was referred for cardiology consultation for a heart murmur. During the visit the patient denied any cardiovascular symptoms. Her physical exam revealed a displaced apex beat downward and to the left and a holosystolic murmur loudest at the apex and radiating to the axilla. An echo was obtained showing LV dilation and systolic dysfunction due to primary myocardial disease, annular dilation with severe loss of central coaptation of the mitral leaflets, and an estimated regurgitant fraction of 55%. In addition, there was systolic flow reversal in the pulmonary veins. According to the ACC/AHA Stages for IMR, at which of the following stages would this patient be?

- A. Stage A
- B. Stage B1
- C. Stage B2
- D. Stage C
- E. Stage D

49-7. A 65-year-old woman with a prior history of myocardial infarction and multivessel PCI was referred for cardiology consultation for a 3-month history of progressive exertional dyspnea despite optimal guideline-directed medical therapy. Her physical examination revealed an irregularly irregular pulse, a displaced apex beat downward and to the left, an elevated JVP, and a holosystolic murmur loudest at the apex and radiating to the axilla. An ECG was obtained and revealed atrial fibrillation (AF). An echo was also obtained showing regional wall motion abnormalities with reduced LV systolic function and LV dilation with severe tethering of mitral leaflets, and an estimated regurgitant volume of 50 mL. A dense, triangular continuous-wave Doppler profile was also noted. Which of the following statements about this patient's AF is *false*?

- A. AF is present in up to 20% of patients undergoing MV surgery
- B. AF may be a marker of disease progression in IMR
- C. AF may be a marker of worse prognosis in IMR
- D. Surgical approaches for AF can be considered in patients undergoing MV surgery
- E. The duration of preoperative AF is a risk factor for recurrence after the MAZE procedure

49-8. Although a variety of percutaneous therapies for MR have been developed, the MitraClip system has emerged clinically as the most tolerated and effective approach to date. Which of the following statements about MitraClip is *false*?

- A. It may be used in high-risk or inoperable patients with severe MR and suitable anatomic criteria
- B. It is currently approved for use in symptomatic patients with primary (degenerative) MR who are at prohibitive risk for surgery
- C. It is currently approved for the treatment of IMR in the United States
- D. It has already received a class IIb recommendation from the European Society of Cardiology for secondary MR
- E. Approximately two-thirds of the MitraClip procedures have been performed in patients with secondary MR worldwide

49-9. A 67-year-old man with a prior history of ischemic heart failure was referred for cardiology consultation for a 2-month history of dyspnea on minimal exertion despite optimal guideline-directed medical therapy for HF. During the visit, the patient had a fast radial pulse with a reduced pulse pressure, the apex beat was displaced downward and to the left, JVP was elevated, and there was a holosystolic murmur loudest at the apex and radiating to the axilla. In addition, an S3 gallop was present. An echo was obtained showing LV dilation and systolic dysfunction, annular dilation with severe loss of central coaptation of the mitral leaflets, a vena contracta width of 0.8 cm, and an estimated regurgitant fraction of 70%. After careful review, the patient's cardiologist decided to refer the patient for surgery as per the ACC/AHA guidelines (class of recommendation: IIb; level of evidence: B).¹ In the setting of severe IMR, which of the following statements about the role of MV repair versus MV replacement (MVR) is *false*?

- A. Repair may be safer with lower perioperative mortality and morbidity
- B. There is a lower rate of recurrent MR with MV repair than with MV replacement
- C. No differences in survival have been reported between the two strategies
- D. No differences exist between the two strategies in the incidence of major adverse cardiac and cerebrovascular events
- E. More adverse events related to HF and cardiovascular readmissions occur for MR repair

49-10. Many observational studies have identified echocardiographic predictors of recurrent MR following MV annuloplasty. In the randomized trial of repair versus replacement, which of the following factors was significantly associated with recurrent moderate or severe MR in patients following repair for severe IMR?

- A. LV end-diastolic diameter > 65 mm

- B. Coaptation depth > 1 cm
- C. Systolic sphericity index > 0.7
- D. Basal aneurysms and dyskinesis
- E. All of the above

ANSWERS

49-1. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 49*) The clinical presentation and the echo findings are consistent with stage A, which includes asymptomatic patients at risk of MR, as is the case for this patient (option A). Stages B (option B), C (options C and D), and D (option E) typically include patients with progressive MR, asymptomatic patients with severe disease, and symptomatic subjects with severe MR, respectively. Options B through E are therefore not correct. Stages of secondary MR with associated valve anatomy, valve hemodynamics, cardiac findings, and symptoms are presented in [Table 49-1](#).¹

TABLE 49-1 Stages of Secondary Mitral Regurgitation with Associated Valve Anatomy, Valve Hemodynamics, Cardiac Findings, and Symptoms

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	<ul style="list-style-type: none"> Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy 	<ul style="list-style-type: none"> No MR jet or small central jet area < 20% LA on Doppler Small vena contracta < 0.30 cm 	<ul style="list-style-type: none"> Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities Primary myocardial disease with LV dilation and systolic dysfunction 	<ul style="list-style-type: none"> Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	<ul style="list-style-type: none"> Regional wall motion abnormalities with mild tethering of mitral leaflet Annular dilation with mild loss of central coaptation of the mitral leaflets 	<ul style="list-style-type: none"> ERO < 0.20 cm^{2†} Regurgitant volume < 30 mL Regurgitant fraction < 50% 	<ul style="list-style-type: none"> Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease 	<ul style="list-style-type: none"> Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	<ul style="list-style-type: none"> Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets 	<ul style="list-style-type: none"> ERO ≥ 0.20 cm^{2†} Regurgitant volume ≥ 30 mL Regurgitant fraction ≥ 50% 	<ul style="list-style-type: none"> Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease 	<ul style="list-style-type: none"> Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	<ul style="list-style-type: none"> Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets 	<ul style="list-style-type: none"> ERO ≥ 0.20 cm^{2†} Regurgitant volume ≥ 30 mL Regurgitant fraction ≥ 50% 	<ul style="list-style-type: none"> Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease 	<ul style="list-style-type: none"> HF symptoms due to MR persist even after revascularization and optimization of medical therapy Decreased exercise tolerance Exertional dyspnea

Reproduced with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014 Jun 10;63(22):2438-2488.

*Several valve hemodynamic criteria are provided for the assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crescentic shape of the proximal convergence.

- 49-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 49*) The magnitude of risk is proportional to the severity of MR (option A is thus incorrect).^{2,3} Although even mild MR is associated with increased mortality, prognosis is particularly poor for patients with severe IMR, with 1-year mortality estimates ranging from 15% to 40% (option B is thus incorrect).⁴ Adverse outcomes are associated with a smaller calculated effective regurgitant orifice (ERO) of > 0.2 cm² in IMR compared to primary MR (option D is thus incorrect).¹ The role and expected benefits of concomitant mitral valve replacements remain controversial in moderate secondary mitral valve lesions such as IMR.
- 49-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 49*) The desirable anatomic criteria for percutaneous edge-to-edge repair of MR using MitraClip may include coaptation length ≥ 2 mm (option A), flail width < 15 mm (option C), MV orifice area > 4 cm² (option D), and MV leaflet length > 1 cm (option E). A short posterior leaflet is actually among the undesirable criteria for MitraClip. The correct answer is therefore option B. The favorable and unfavorable anatomic criteria are presented in Table 49-2.⁵

TABLE 49-2 Favorable and Unfavorable Anatomic Criteria for Percutaneous Edge-to-Edge Repair of MR

Anatomical MV and LV Characteristics for Percutaneous Edge-to-Edge Repair of MR	
Desirable Criteria	Undesirable Criteria
<ul style="list-style-type: none"> • Moderate to severe MR (≥ grade 3) • Pathology in the A2-P2 zone • Coaptation length ≥ 2 mm • Flail gap < 10 mm • Flail width < 15 mm • MV orifice area > 4 cm² • MV leaflet length > 1 cm 	<ul style="list-style-type: none"> • Commissural lesion • Short posterior leaflet • Severe asymmetric tethering • Calcification in the grasping area • Severe annular calcification • MV cleft • Severe annular dilation • Severe LV remodeling • Large (> 50%) inter-commissural extension of regurgitant jet • Severe myxomatous degeneration with multi-scallop prolapse

Reproduced with permission from De Bonis M, Al-Attar N, Antunes M, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease, *Eur Heart J*. 2016 Jan 7;37(2):133-139.

- 49-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 49*) The severity of IMR at rest does not necessarily reflect nor predict the severity of MR during exercise (option A is thus false, and therefore the correct answer). Exercise-induced increase in IMR provides additional prognostic information over resting evaluation and identifies patients at higher risk of adverse clinical outcomes (option B is thus incorrect).⁶ For example, an increase in EROA of ≥13 mm² during exercise is associated with increased mortality and HF hospitalizations (options D and E are thus incorrect).⁷ Exercise echocardiography has been proposed to evaluate patients with exertional dyspnea out of proportion to the degree of resting IMR (option C is thus incorrect) and LV dysfunction, patients with IMR and unexplained acute pulmonary edema, and patients with moderate IMR at rest who are due to undergo surgical revascularization with CABG.^{6,8}
- 49-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 49*) Indicators of severe MR should be integrated^[12] and include a peak mitral valve E-wave velocity > 1.2 m/s (not E-wave velocity < 1.2 m/s as stated in option A, which is thus the correct answer), a dense triangular continuous-wave Doppler profile (option B is thus incorrect), vena contracta width ≥ 0.7 cm (option D is thus incorrect), MR regurgitant jet area/left atrial area ratio ≥ 40% (option E is thus incorrect), and systolic flow reversal in the pulmonary veins (option C is thus incorrect).¹⁰
- 49-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 49*) The clinical presentation and the echo findings are consistent with stage C, which includes asymptomatic patients with severe MR as is the case for this patient (option D). Stages A (option A), B (options B and C), and D (option E) typically include patients at risk of MR, patients with progressive MR, and symptomatic patients with severe MR, respectively. Options A, B, C, and E are therefore not correct. Stages of secondary MR with associated valve anatomy, valve hemodynamics, cardiac findings, and symptoms are presented in Table 49-1.¹
- 49-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 49*) Atrial fibrillation (AF) is commonly associated with MR, and it is present in up to 50% of patients undergoing MV surgery (option A is thus false, and therefore is the correct

answer).¹¹ LA chamber enlargement as a consequence of increased pressure and volume load to the LA from MR is implicated in the genesis of AF.¹² AF may be a marker of disease progression (option B is thus incorrect) and worse prognosis in IMR (option C is thus incorrect). Surgical approaches for AF with or without left atrial appendage ligation can be considered in patients undergoing MV surgery (option D is thus incorrect). Risk factors for the return of AF after the MAZE procedure include duration of preoperative AF, left atrial size, and reduced LV function (option E is thus incorrect).¹³

- 49-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 49*) The MitraClip is a transcatheter mitral device for use in high-risk or inoperable patients with severe MR and suitable anatomic criteria (option A is true and thus incorrect). It is currently approved by the US Food and Drug Administration for use in symptomatic patients with primary (degenerative) MR who are at prohibitive risk for surgery (option B is thus incorrect); it is not approved for the treatment of IMR in the United States (option C is thus false, and therefore is the correct answer), but is under investigation for this indication through the Clinical Outcomes Assessment of MitraClip Percutaneous Therapy for Extremely High-Surgical-Risk Patients (COAPT) trial.¹⁰ In contrast, the MitraClip system has already received a class IIb recommendation from the European Society of Cardiology for secondary MR (option D is thus incorrect). Worldwide, it is estimated that approximately two-thirds of the MitraClip procedures have been performed in patients with secondary MR (option E is thus incorrect).
- 49-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 49*) In the setting of severe IMR, debate has focused on the role of MV repair versus MV replacement (MVR). Repair has been considered safer with lower perioperative mortality and morbidity (option A is thus incorrect), though generally associated with a higher rate of recurrent MR compared with replacement (option B is thus false, and therefore is the correct answer). A randomized multicenter trial assigned 251 patients with severe IMR to undergo either MV repair ($n = 126$) or chordal-sparing MVR ($n = 125$) and did not demonstrate any significant difference in LV end-systolic volume indexed to body surface area at 1 and 2 years (primary end point). No differences in survival (option C is thus incorrect) or the incidence of major adverse cardiac and cerebrovascular events (option D is thus incorrect) were found. The rate of recurrence of moderate or severe MR was significantly higher in the repair compared to the replacement group (32.6% vs 2.3% at 1 year, $P < .001$; and 58.8% versus 3.8% at 2 years, $P < .001$), resulting in more adverse events related to HF and cardiovascular readmissions (option E is thus incorrect).^{14,4}
- 49-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 49*) Many observational studies have identified echocardiographic predictors of recurrent MR following MV annuloplasty, including an LV end-diastolic diameter > 65 mm (option A), coaptation depth > 1 cm (option B), and systolic sphericity index > 0.7 (option C).⁵ These options (A, B, and C) would be correct in the setting of MV annuloplasty, but this question is about the factors associated with recurrent moderate or severe MR in patients following repair for severe IMR. In the randomized trial of repair versus replacement, only basal aneurysms and dyskinesis were significantly associated with recurrent moderate or severe MR in patients following repair for severe IMR (option D is thus the correct answer).¹⁵ It is important to note that none of the prediction models for recurrent MR have been externally validated. The durability of repair is also influenced by the natural history of underlying ventricular dilation over time; progressive dilation will undermine the integrity of MV repair.

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CHAPTER 50

Mitral Stenosis

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 50-1.** Rheumatic heart disease (RHD) remains prevalent in developing countries. Which of the following statements about RHD in developing countries is *false*?
- A. The prevalence ranges from 1 to 2 per 1000 school children
 - B. Ten percent of patients with RHD have isolated MS
 - C. Only 10% of patients with isolated MS report a past history of rheumatic fever
 - D. Symptoms occur after at least 4 decades from the initial attack of ARF
 - E. All of the above
- 50-2.** A 52-year-old woman with a prior history of type 2 diabetes, depression, and SLE presented to her family physician for a routine visit. The patient denied any symptoms such as exertional dyspnea, chest pain, or palpitations. Physical examination revealed a loud first heart sound and a middiastolic rumble. A transthoracic echocardiogram was performed and showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 1.8 cm^2 , and a diastolic pressure half-time of 145 ms. The patient was in normal sinus rhythm and had a valve morphology that was suitable for BMV. According to the ACC/AHA Stages for MS, at which of the following stages would this patient be?
- A. Stage A
 - B. Stage B
 - C. Stage C1
 - D. Stage C2
 - E. Stage D
- 50-3.** A 56-year-old woman with no prior medical history was referred for cardiac consultation following a 6-month history of exertional dyspnea. Physical examination revealed a loud P2 and a middiastolic rumble. A transthoracic echocardiogram was performed that showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 0.9 cm^2 , a diastolic pressure half-time of 230 ms, and a PASP of 69 mm Hg. In addition, there was right ventricular dilatation and dysfunction. Which of the following statements about this patient's pulmonary hypertension is *false*?
- A. Secondary vasoconstriction in the pulmonary bed may play a role in its development
 - B. The specific cause of the observed pulmonary vasoconstriction is well established
 - C. It is almost always reversed by relief of MS
 - D. It can be improved by the administration of sildenafil
 - E. The nitric oxide pathway may be involved in the mechanism of pulmonary vasoconstriction
- 50-4.** A 19-year-old man with a prior history of acute rheumatic fever presented to the emergency department complaining of dyspnea on minimal exertion, orthopnea, and paroxysmal nocturnal dyspnea. Physical examination revealed a loud first heart sound and a low-pitched diastolic rumble best heard at the apex. The initial investigations, including a chest x-ray, were consistent with the diagnosis of pulmonary edema. A transthoracic echocardiogram was performed and showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and an MVA of 1.2 cm^2 with a PASP of 62 mm Hg. Which of the following statements about this patient is *false*?
- A. Juvenile MS is the most likely diagnosis
 - B. The likely diagnosis may constitute up to a quarter of rheumatic MS cases in developing countries
 - C. Boys are more commonly affected
 - D. Atrial fibrillation is uncommon
 - E. MV calcification and LA thrombi are common findings

- 50-5.** A 28-year-old primigravid woman at 31 weeks' gestation was admitted to the hospital because of NYHA class II heart failure symptoms. Physical examination revealed a loud first heart sound and a middiastolic rumble. An initial ECG revealed AF with fast ventricular response. A transthoracic echocardiogram was performed; it showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and a diastolic pressure half-time of 138 ms. The patient had a valve morphology that was suitable for BMV. Which of the following will *not* be appropriate as an initial next best step?
- Diuretics
 - Restriction of physical activity
 - Metoprolol
 - Digoxin
 - BMV
- 50-6.** A 55-year-old woman with a prior history of acute rheumatic fever at age 15 presented to the emergency department complaining of exertional dyspnea and intermittent palpitations. Physical examination revealed a loud first heart sound and a middiastolic rumble. In addition, there was an irregularly irregular pulse. Atrial fibrillation was confirmed on the initial ECG. A transthoracic echocardiogram was performed and revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and an MVA of 1.1 cm^2 . In addition there were extensive calcifications and severe subvalvular disease. Which of the following would be the surgical treatment of choice for this patient?
- Closed mitral valvotomy (CMV)
 - Open mitral valvotomy (OMV)
 - Mitral valve replacement (MVR)
 - BMV
 - All of the above
- 50-7.** A 49-year-old woman with no prior medical history presented to her cardiologist complaining of a reduced exercise tolerance. Physical examination revealed a loud first heart sound and a middiastolic rumble. A transthoracic echocardiogram was performed and showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 1.1 cm^2 , a diastolic pressure half-time of 210 ms, and a PASP of 49 mm Hg. The patient was in normal sinus rhythm and had a valve morphology that was suitable for BMV. According to the ACC/AHA Stages for MS, at which of the following stages would this patient be?
- Stage A
 - Stage B
 - Stage C1
 - Stage C2
 - Stage D
- 50-8.** Relief of MS by surgery may be done either by CMV, OMV, or MVR. Which of the following is a class 2b indication for MVR?
- Severely symptomatic MS (MVA $< 1.5 \text{ cm}^2$; NYHA class III/IV) who are not high risk for surgery and who are not candidates for BMV
 - Severe symptomatic MS (MVA $< 1.5 \text{ cm}^2$; NYHA class III/IV) who are not high risk for surgery and who have failed previous BMV
 - Severe MS (MVA $\leq 1.5 \text{ cm}^2$) with recurrent embolic events despite adequate anticoagulation
 - Severe MS (MVA $< 1.5 \text{ cm}^2$) undergoing aortic valve surgery
 - Severe MS (MVA $< 1.5 \text{ cm}^2$) undergoing CABG
- 50-9.** A 62-year-old woman with no prior medical history was referred for cardiac consultation following a 6-month history of exertional dyspnea and intermittent palpitations. Physical examination revealed an irregularly irregular pulse, a loud P2 and a middiastolic rumble. In addition, the assessment of the jugular venous pressure revealed absent "a" wave and "x" descent. The initial ECG confirmed AF. A transthoracic echocardiogram was performed, and it showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 0.7 cm^2 , a diastolic pressure half-time of 240 ms, and a PASP of 79 mm Hg. In addition, there was right ventricular dilatation and dysfunction. Which of the following statements about this patient's AF is *false*?
- The prevalence in MS patients is approximately 40%
 - Age and the severity of MS are the most important determinants for the development of AF
 - LA enlargement is the cause of AF rather than the result of AF
 - AF in MS may also be secondary to rheumatic scarring and histologic changes in the LA
 - Relief of mitral obstruction may or may not prevent AF
- 50-10.** The echocardiogram is the modality of choice in the assessment of MS. In terms of the assessment of the valve area, which of the following echo modalities has the closest agreement with invasive Gorlin-derived MVA?

- A. Direct 2D planimetry
- B. Direct 3D planimetry
- C. Continuity equation method
- D. Pressure half-time technique
- E. Proximal isovelocity surface area (PISA) method

ANSWERS

50-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 50*) Using echocardiographic screening, the prevalence of RHD ranges from 20 to 30 per 1000 school children (option A is thus not correct).^{1,2} This leads to a large pool of rheumatic MS. Forty percent of patients with RHD have isolated MS (option B is thus not correct) but only 60% of these patients report a past history of rheumatic fever (option C is also not correct).^{2,3} In developing countries, the disease may progress much more rapidly, leading to symptoms by the age of 20 (juvenile MS), often within five years of the initial attack of RF (option D is thus not correct).⁴ All the above statements are false, and therefore, the best option is E.

50-2. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 50*) The clinical presentation and the echo findings are consistent with stage B, which includes patients with progressive MS (not severe). Stages A, C, and D typically include patient at risk of MS, asymptomatic patients but with severe disease, and symptomatic subjects with severe MS, respectively. Therefore, options A, C, D, and E are not correct. The stages and severity of MS are presented in [Table 50-1](#).⁵

TABLE 50-1 Stages and Severity of Mitral Stenosis

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	Mild diastolic valve doming	Normal transmitral flow velocity	None	None
B	Progressive MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimtered MVA $> 1.5 \text{ cm}^2$	1. Increased transmitral flow velocities 2. MVA $> 1.5 \text{ cm}^2$ 3. Diastolic pressure half-time $< 150 \text{ ms}$	1. Mild-to-moderate LA enlargement 2. Normal pulmonary pressure at rest	None
C	Asymptomatic severe MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimtered MVA $\leq 1.5 \text{ cm}^2$ (MVA $\leq 1.0 \text{ cm}^2$ with very severe MS)	1. MVA $\leq 1.5 \text{ cm}^2$ (MVA $\leq 1.0 \text{ cm}^2$ with very severe MS) 2. Diastolic pressure half-time $\geq 150 \text{ ms}$ (diastolic pressure half-time $\geq 220 \text{ ms}$ with very severe MS)	1. Severe LA enlargement 2. Elevated PASP $> 30 \text{ mm Hg}$	None
D	Symptomatic severe MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimtered MVA $\leq 1.5 \text{ cm}^2$	1. MVA $\leq 1.5 \text{ cm}^2$ (MVA $\leq 1.0 \text{ cm}^2$ with very severe MS) 2. Diastolic pressure half-time $\geq 150 \text{ ms}$ (diastolic pressure half-time $\geq 220 \text{ ms}$ with very severe MS)	1. Severe LA enlargement 2. Elevated PASP $> 30 \text{ mm Hg}$	1. Reduced exercise tolerance 2. Exertional dyspnea

MVA, Mitral valve area.

(Data from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol*. 2014 Jun 10;63(22):2438-2488.)

50-3. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 50*) The force needed to overcome the increased LA pressure and to drive blood past the stenotic mitral valve is generated by the right ventricle (RV), such that right ventricular pressure and pulmonary pressure become elevated. As MS becomes severe, secondary vasoconstriction in the pulmonary bed causes a further increase in pulmonary artery pressure (option A is thus incorrect), and pulmonary hypertension may become extreme. The exact cause of pulmonary vasoconstriction in MS is unknown (option B is thus false and is the correct answer). It is known that pulmonary hypertension is usually reversed by relief of MS (option C is thus incorrect)⁶ and also that it can at times be improved by the administration of phosphodiesterase inhibitors such as sildenafil (option D is thus incorrect)⁷ or by nitric oxide inhalation.⁸ These data suggest that the nitric oxide pathway is in some way involved in the mechanism of pulmonary vasoconstriction and pulmonary hypertension in MS (option E is thus incorrect). Occasionally, patients have structural changes in the pulmonary bed, leading to a disproportionate pulmonary hypertension that is not completely resolved with relief of MS.

- 50-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 50*) This patient suffers from rheumatic mitral stenosis, which when presenting below 20 years is termed juvenile MS as in this case (option A is thus incorrect).⁴ This condition is uncommon in developed countries, but it may constitute up to a quarter of cases of all rheumatic MS in developing countries (option B is thus incorrect).⁴ Unlike in adults, boys are more commonly affected (option C is thus incorrect).⁴ Heart failure/pulmonary edema is a frequent finding, while atrial fibrillation is uncommon (option D is thus incorrect). Severe pulmonary hypertension is common. Although MV calcification and LA thrombi are absent (option E is false and is thus the correct answer), the valve morphology is associated with severe subvalvular disease and thickened leaflets.
- 50-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 50*) Diuretics can usually be used safely to control mild symptoms; thus they should be administered as part of the initial management (option A). Overaggressive use of diuretics can lead to placental hypoperfusion. Therapy is targeted to reduce heart rate and prolong diastolic filling period. This includes restrictions on physical activity (option B) and the use of beta-blockers (those with selective beta-1 activity is preferred). Metoprolol is preferred over atenolol because it has a lower incidence of intrauterine growth retardation (option C).⁵ In patients with atrial fibrillation, digoxin can be safely used (option D). Pregnant patients with severe MS (MVA ≤ 1.5 cm²) and mild symptoms are best managed medically (options A, B, C, and D are thus true), while those who continue to manifest severe symptoms (NYHA class III-IV) despite medical therapy should undergo BMV if the valve is suitable (option E).⁵
- 50-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 50*) Relief of MS by surgery may be done either by CMV (option A), OMV (option B), or MVR. CMV, via the transatrial or transventricular route, is still practiced successfully in many developing countries. However, the results of BMV are superior to CMV with lower morbidity. When extensive calcification and severe subvalvular disease make BMV/OMV unfeasible (option D), as in this case, MVR is the surgical treatment of choice (option C).
- 50-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 50*) The clinical presentation and the echo findings are consistent with stage D, which includes symptomatic patients with severe MS (option E). Stages A, B, and C typically include patient at risk of MS, patient with progressive MS, and asymptomatic patients but with severe disease, respectively. Therefore, options A, B, C, and D are not correct. The stages and severity of MS are presented in [Table 50-1](#).⁵
- 50-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 50*) The indications for MVR are as follows:⁵ (1) Severely symptomatic patients (NYHA class III/IV) with severe MS (MVA < 1.5 cm²) who are not high risk for surgery and who are not candidates for, or have failed, previous BMV (options A and B, respectively) are class 1 indications, not class 2b; (2) severe MS (MVA < 1.5 cm²) patients undergoing other cardiac surgery (eg, aortic valve surgery, CABG), which are options D and E respectively, are class 2a indications; and (3) mitral valve surgery and LAA excision may be considered for patients with severe MS (MVA ≤ 1.5 cm², stages C and D) with recurrent embolic events despite adequate anticoagulation (option C); these are class 2b indications, and therefore C is the correct answer.
- 50-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 50*) Atrial fibrillation is the most common complication of MS, developing in approximately 40% of patients (option A is thus incorrect).⁹ Age and the severity of MS are the most important determinants for the development of AF (option B is thus incorrect).¹⁰ AF is related to LA enlargement, the latter often a result rather than the cause of AF (option C is thus false and is therefore the correct answer for this question).¹¹ Although it is often hoped that relief of MS will result in restoration of sinus rhythm, AF in MS is due not only to increased LA size but also to rheumatic scarring and histologic changes in the LA.¹² Thus relief of mitral obstruction may¹³ or may not prevent AF¹⁴ or allow for a return to sinus rhythm (option E is thus incorrect).
- 50-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 50*) Valve area can be estimated by direct planimetry (either 2D or 3D), by the continuity equation, by the pressure half-time technique (dividing an empirical constant of 220 by the mitral inflow pressure half-time), and by the PISA method. In some cases these measures are concordant, but in others, all measures must be taken into account and clinical judgment used to decide on MS severity. Planimetry by three-dimensional echocardiography (option B) has better reproducibility than two-dimensional echocardiography (option A) and has the closest agreement with invasive Gorlin-derived MVA.¹⁵ Options C, D, and E are not correct for the above-mentioned reasons.

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CHAPTER 51

Tricuspid and Pulmonary Valve Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 51-1.** A 15-year-old boy with a prior medical history of childhood murmur presented to the emergency department after a series of presyncopal episodes. The physical examination revealed a systolic ejection click, a loud systolic murmur peaking in late systole as well as a soft P2. Initial ECG and chest radiography showed evidence of right heart chamber enlargement. An echocardiogram was obtained and showed doming and restricted opening of the pulmonary valve. In addition, spectral and color-flow Doppler revealed high-velocity turbulent flow in the main pulmonary artery consistent with pulmonary stenosis. The patient underwent cardiac catheterization, which revealed an RV-to-pulmonary artery peak-to-peak gradient of 37 mm Hg. Which of the following would be the best step in the management of this patient?
- A. Medical therapy with follow-up
 - B. Surgical valvotomy
 - C. Percutaneous balloon valvotomy
 - D. Bioprosthetic valve replacement
 - E. Mechanical valve replacement
- 51-2.** In which of the following settings is surgical correction of tricuspid valve regurgitation (TR) most commonly performed?
- A. Isolated procedure for primary TR
 - B. Isolated procedure for secondary TR
 - C. Concomitant procedure during mitral valve surgery
 - D. Concomitant procedure during aortic valve surgery
 - E. Concomitant procedure during coronary artery bypass grafting
- 51-3.** A 19-year-old man with no known medical history presented to the emergency department complaining of flushing, diarrhea, and dyspnea. The cardiovascular examination revealed a 2/6 decrescendo diastolic murmur at the left upper sternal border, along with an RV heave and an elevated JVP. An echocardiogram demonstrated thickened barely mobile pulmonary valve cusps, with severe pulmonary regurgitation; subcostal imaging incidentally reveals a hepatic mass. Which of the following is the most likely diagnosis?
- A. Infective endocarditis
 - B. Viral gastroenteritis
 - C. Congenital pulmonary insufficiency
 - D. Rheumatic heart disease
 - E. Carcinoid disease
- 51-4.** An asymptomatic 47-year-old man with a remote history of rheumatic fever as a child is found to have a diastolic murmur during a routine physical examination; the murmur is best heard at the left lower sternal border and increases on inspiration. He is referred for an echocardiogram, which shows a thickened, distorted tricuspid valve with moderate tricuspid stenosis and mild-to-moderate tricuspid regurgitation. Which of the following statements regarding rheumatic tricuspid valve disease is *false*?
- A. Rheumatic involvement of the tricuspid valve is more common than the aortic valve
 - B. Tricuspid stenosis and regurgitation are often seen in combination
 - C. A Kussmaul sign may be appreciated on examination
 - D. Valve repair with balloon valvotomy or annuloplasty is preferred in cases where the valve is not severely distorted
 - E. When valve replacement is needed, a bioprosthesis is preferred over a mechanical prosthesis
- 51-5.** A 25-year-old woman with no significant past medical history was referred to the cardiology clinic complaining of a 6-month history of exertional chest discomfort. The physical examination revealed a systolic murmur peaking in late systole

and best heard over the pulmonary area, and a well-preserved but delayed P2. Initial ECG and chest radiography showed evidence of right heart chamber enlargement. An echocardiography was obtained and showed normal pulmonary valve cusps, midsystolic cusp closure, a prominent presystolic a-wave, and a normal main pulmonary artery diameter. In addition, spectral and color-flow Doppler revealed a late-peaking, high-velocity flow with turbulence in the right ventricular outflow tract. Which of the following is the most likely diagnosis?

- A. Pulmonary valve stenosis
- B. Infundibular pulmonary stenosis
- C. Pulmonary regurgitation
- D. Idiopathic pulmonary artery dilatation
- E. Pulmonary valve endocarditis

51-6. A 19-year-old woman is followed in cardiology clinic for pulmonary valve stenosis, but she has missed her last appointments because she “felt fine.” She now notes progressive exertional dyspnea and can no longer play sports with her friends. Four years ago, the physical examination revealed a systolic ejection click, a preserved but delayed P2, and a 2/6 systolic murmur peaking in early-to-mid systole that was best heard over the pulmonary area. Given the clinical suspicion of worsening pulmonary valve stenosis, which of the following physical examination findings would *not* be expected at this time?

- A. Murmur has gotten louder
- B. Murmur peaks later in systole
- C. Systolic ejection click is more prominent in inspiration
- D. P2 has gotten softer
- E. All of the above

51-7. A 67-year-old man with a remote history of pulmonary emboli complains of increased abdominal girth. A physical examination revealed elevated JVP, systolic RV heave, a 3/6 pansystolic murmur best heard at the left lower sternal border, and ascites. An echo showed right ventricular dilation, tricuspid annular dilation with loss of central coaptation of the tricuspid leaflets, and a vena contracta width of 0.8 cm. The findings were consistent with severe functional tricuspid regurgitation, and loop diuretic therapy is prescribed. Which of the following statements about tricuspid regurgitation (TR) is *false*?

- A. If treated medically, this patient will have a mortality of 26% at 5 years
- B. Cardiac MRI may be considered for the assessment of RV size and function
- C. Aldosterone antagonists may be of additive benefit, especially in the setting of hepatic congestion
- D. Pulmonary vasodilators may be helpful
- E. None of the above

51-8. A 55-year-old woman with a prior history of myxomatous mitral valve disease, having been lost to follow-up, presented to the emergency department complaining of dyspnea on minimal exertion and leg swelling. Physical examination revealed a 4/6 systolic murmur best heard at the apex, along with an elevated JVP, pitting leg edema, and mild ascites. An echo was obtained showing biventricular dilation and systolic dysfunction, severe mitral regurgitation, and moderate functional tricuspid regurgitation. The tricuspid leaflets were tethered, but the annular diameter was within normal limits. Which of the following would be the best recommendation according to current guidelines?

- A. Mitral valve surgery only
- B. Mitral valve surgery with tricuspid valve replacement
- C. Mitral valve surgery with tricuspid annuloplasty
- D. Medical therapy with aggressive diuresis
- E. Isolated tricuspid annuloplasty

51-9. The recommendation to offer surgical correction of the mitral and tricuspid valve lesions is discussed with the patient in Question 8. She asks about the success rate of the additional tricuspid valve procedure being recommended. Which of the following best approximates the probability that this patient will be free from significant tricuspid regurgitation 5 to 10 years post-annuloplasty?

- A. 20%
- B. 40%
- C. 60%
- D. 85%
- E. 95%

51-10. Because tricuspid regurgitation is a dynamic lesion, tricuspid regurgitation may be graded as moderate or severe on preoperative transthoracic echocardiography under normal loading conditions, but it may appear only mild on intraoperative transesophageal echocardiography under general anesthesia. Other than tricuspid regurgitation severity under normal loading conditions, which of the following parameters should be taken into account when deciding about the need for concomitant tricuspid annuloplasty at the time of mitral valve repair?

- A. Annular dimensions
- B. Leaflet malcoaptation or leaflet-annulus mismatch on direct inspection
- C. The presence of pulmonary hypertension
- D. The presence of atrial fibrillation
- E. All of the above

ANSWERS

- 51-1. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 51*) According to the American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease,¹ balloon valvotomy is recommended in adolescent and young adult patients with pulmonic stenosis who have exertional dyspnea, angina, syncope, or presyncope and an RV-to-pulmonary artery peak-to-peak gradient greater than 30 mm Hg at catheterization (Class I and Level of Evidence: C). Moderately severe and severe pulmonary valve stenosis is currently treated by percutaneous balloon valvotomy (option C). Surgical valvotomy or replacement is rarely needed (options B, D, E). There is no effective medical therapy for this structural condition (option A).
- 51-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 51*) Surgical correction of tricuspid valve disease is most commonly performed at the time of mitral valve surgery (option C).² Significant TR is less frequently observed in patients with aortic valve or ischemic heart disease, and therefore tricuspid valve surgery is less often needed at the time of these surgeries (options D, E). Furthermore, the majority of patients with TR, whether primary or secondary, are effectively managed medically with diuretics, such that tricuspid valve surgery is not often performed as an isolated procedure, unless it is refractory to medical therapy (options A, B).
- 51-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 51*) The patient is presenting with cutaneous (flushing) and gastrointestinal (diarrhea) symptoms that are typical of the carcinoid syndrome. The pathognomonic echocardiographic appearance of markedly thickened retracted leaflets is more common on the tricuspid valve but is also observed on the pulmonary valve, as in this case. The gold standard treatment for carcinoid heart disease is usually tricuspid valve replacement and pulmonary valve replacement with patch enlargement of the right ventricular outflow tract. Endocarditis does not have this echocardiographic appearance and is not suspected in the absence of fever (option A). Viral gastroenteritis is not associated with these cardiac findings (option B) whereas congenital pulmonary insufficiency is not associated with these noncardiac findings (option C). Rheumatic involvement of the pulmonary valve may manifest as thickening and restriction at the commissural level, and it would typically be associated with the involvement of other valves without the cutaneous and gastrointestinal symptoms (option D).
- 51-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 51*) Rheumatic involvement of the tricuspid valve is far less common than with the mitral and the aortic valves (option A), reported in between 10% and 20% of patients. Rheumatic tricuspid valve disease is often predominantly functional, but it is occasionally characterized by leaflet involvement with thickened, fibrosed, and shortened leaflets, and commissural fusion. The resulting clinical syndrome is one of mixed stenosis and regurgitation (option B). Inspiratory increase in jugular venous pressure is common and simulates the Kussmaul sign in constrictive pericarditis (option C). However, the jugular venous pulse with rheumatic tricuspid valve stenosis and regurgitation fails to show rapid "y" descent. Treatment of rheumatic tricuspid valve disease consists of balloon valvotomy for predominant stenosis, valve repair with annuloplasty (option D), or valve replacement with a low-profile bioprosthetic valve for severely distorted valves (option E).
- 51-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 51*) Although the valve cusps are normal in infundibular stenosis, a characteristic midsystolic cusp closure (caused by dynamic subvalvular obstruction) and prominent presystolic a-wave are often diagnostic clues, along with high-velocity turbulent flow in the right ventricular outflow tract. The pulmonary valve morphology shows doming and restricted opening in the presence of pulmonary valve stenosis, with high-velocity turbulent flow in the main pulmonary artery (option A). The pulmonary artery and branches are dilated in pulmonary hypertension, idiopathic pulmonary artery dilatation, and severe pulmonary regurgitation (options C and D). In cases of pulmonary valve endocarditis, a mobile vegetation may be observed (option E).
- 51-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 51*) With progressive pulmonary valve stenosis severity, the murmur gets louder, longer, and peaks later in systole (options A and B). The ejection click is often more prominent in expiration (option C). This seemingly paradoxical behavior of the pulmonary ejection click is explained by an inspiratory increase in right ventricular end-diastolic pressure, which opens the valve in late diastole and hence the absence of systolic ejection clicks during the inspiratory phase. The pulmonary component of the second heart sound (P2) becomes softer (option D), and in very severe cases, the murmur spills past the aortic component, and the pulmonary component is inaudible.
- 51-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 51*) Several large studies have reported on the adverse effects of longstanding tricuspid regurgitation.³⁻⁵ If treated medically, moderate to severe tricuspid regurgitation carries a

mortality of 26% at 5 years (option A). In addition to echocardiography, cardiac MRI can provide complementary information about the severity of tricuspid regurgitation and its impact on RV dilation and dysfunction (option B). The mainstay of medical management for functional tricuspid regurgitation includes loop diuretics and aldosterone antagonists to decrease volume overload in patients with peripheral edema and ascites (option C).¹ Specific pulmonary vasodilators may be helpful to reduce right ventricular afterload in patients with reversible pulmonary hypertension evaluated with cardiac catheterization (option D).

- 51-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 51*) According to the American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease,¹ tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional tricuspid regurgitation at the time of left-sided valve surgery, with either (1) tricuspid annular dilatation or (2) prior evidence of right heart failure (Class IIa and Level of Evidence: B). This patient has evidence of right heart failure, and therefore should be considered for tricuspid annuloplasty (option C), which would also be a consideration if she had evidence of annular dilatation.⁶ Tricuspid valve replacement (option B) is not indicated for the repair of moderate functional regurgitation because it introduces the additional risks of thromboembolic and hemorrhagic complications inherent with mechanical prostheses, or the risk of structural valve degeneration requiring reoperation inherent with bioprostheses.⁷ Isolated tricuspid valve surgery (option E) is not appropriate because this patient has severe symptomatic mitral regurgitation that requires correction. Medical therapy is not a curative option for this patient (option D).
- 51-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 51*) Data from the surgical literature suggest that 85% of patients having a ring annuloplasty for functional tricuspid regurgitation will be free from moderate or severe tricuspid regurgitation from 5 to 10 years after surgery (option D).⁸ Risk factors for recurrent moderate or severe tricuspid regurgitation include: higher preoperative regurgitation grade, poor left ventricular function, permanent pacemaker, and repair type other than ring annuloplasty.⁹
- 51-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 51*) In this context, the final decision should be guided not only by the degree of regurgitation but also by annular enlargement (diameter > 7 cm from the anteroseptal to anteroposterior commissures when measured by direct inspection, or > 40 mm from the 4-chamber view when measured by echo), leaflet malcoaptation, and the presence of atrial fibrillation, pulmonary hypertension, right ventricular dysfunction, or left ventricular dysfunction.

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CHAPTER 52

Prosthetic Heart Valves

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 52-1.** A 62-year-old man with a prior history of infective endocarditis and a porcine aortic bioprosthesis that was implanted 12 weeks ago attended the cardiology clinic for a routine visit. At the clinic, a complete evaluation was unremarkable, including anticoagulation adherence, clinical questioning, physical examination, 12-lead ECG, and transthoracic echocardiography for the assessment of ventricular and prosthetic valve function. Which of the following actions would be the most appropriate at this time?
- A. Discharge the patient from the clinic
 - B. Discharge the patient from the clinic with family physician follow-up
 - C. Discharge the patient from the clinic and advise him to get in touch if symptoms occur
 - D. Follow the patient for another year, and if he is stable, discharge him with family physician follow-up
 - E. None of the above
- 52-2.** Having undergone an echocardiogram before and shortly after his aortic valve replacement surgery, the patient described in Question 52-1 would like to know when the next echocardiogram will be scheduled. Which of the following statements about the use of transthoracic echocardiography after the bioprosthetic valve replacement is *false*?
- A. Should be performed annually after the 10th postoperative year
 - B. Should be performed annually after the fifth postoperative year
 - C. Should be performed annually after the second or third postoperative year in patients who are at higher risk of accelerated valve dysfunction
 - D. Should be performed sooner if new symptoms occur
 - E. All of the above
- 52-3.** A 60-year-old man with a past medical history of a mechanical mitral valve replacement presents to the cardiology clinic and would like to have an expert opinion regarding antibiotic prophylaxis before dental procedures. Which of the following would be the best recommendation regarding antibiotic prophylaxis?
- A. 2 g of amoxicillin before any dental procedure
 - B. 2 g of ampicillin before any dental procedure
 - C. 600 mg of clindamycin before any dental procedure
 - D. Antibiotic prophylaxis is no longer recommended
 - E. Antibiotic prophylaxis only if there is manipulation of gingival or periapical tissue, or perforation of oral mucosa
- 52-4.** You receive a phone call from a urologist for a consultation regarding a 55-year-old man with a past medical history of a bioprosthetic aortic valve replacement. The patient is scheduled to undergo a cystoscopy as part of his investigation for bladder cancer. Which of the following would be the best recommendation regarding antibiotic prophylaxis?
- A. 2 g of amoxicillin before the urological procedure
 - B. 2 g of ampicillin before the urological procedure
 - C. 600 mg of clindamycin before the urological procedure
 - D. Antibiotic prophylaxis is no longer recommended
 - E. Cancel the cystoscopy and advise alternate noninvasive diagnostic testing
- 52-5.** A 79-year-old man with a prior history of arterial hypertension, dyslipidemia, and stage IV chronic kidney disease presented to the emergency department complaining of worsening dyspnea and decreasing exercise tolerance. The patient underwent bioprosthetic aortic valve replacement 8 years earlier for aortic stenosis. The physical examination revealed reduced carotid upstroke bilaterally and a 5/6 systolic ejection murmur across the precordium. A transthoracic echocardiogram was obtained and revealed severe prosthetic valve stenosis. Which of the following may potentially explain

the echocardiographic findings?

- A. Bioprosthetic valve degeneration
- B. Bioprosthetic valve thrombosis
- C. Endocarditis with a large burden of vegetation
- D. Pannus
- E. All of the above

52-6. A 65-year-old woman with a prior history of arterial hypertension, coronary heart disease, and depression is referred for a routine echocardiogram 4 weeks after having undergone an aortic valve replacement with a 21-mm bioprosthesis. The echocardiogram revealed normal left ventricular function with a mean transprosthetic gradient of 68 mm Hg, and a calculated indexed effective orifice area was $0.61 \text{ cm}^2/\text{m}^2$. The mobility of prosthetic leaflets was normal, and there were no findings to suggest prosthetic pannus or thrombus. Patient-prosthesis mismatch was suspected. Which of the following may *not* be a clinical consequence of this diagnosis?

- A. Decreased cardiac index
- B. Reduced functional improvement
- C. Higher risk of stroke in the first 30 days
- D. Less left ventricular mass regression
- E. More adverse events in long-term follow-up

52-7. A 37-year-old obese man with a history of mechanical mitral valve replacement for congenital mitral valve disease presented to the emergency department complaining of dyspnea. Upon further questioning, the patient also reported a prior history of four embolic strokes with no residual neurologic deficit, all of which were related to poor medication adherence. The physical examination revealed 4/6 systolic ejection murmur across the precordium. A transthoracic echocardiography was obtained and revealed prosthetic valve thrombosis. Which of the following is the strongest independent predictor of nonadherence to an anticoagulation regimen?

- A. Age less than 55 years
- B. Age older than 55 years
- C. Living in a rural geographic area
- D. Living in an urban geographic area
- E. Pregnancy in the first trimester

52-8. A 42-year-old woman has a history of bioprosthetic mitral valve replacement 12 years ago for myxomatous mitral valve disease (bioprosthesis implanted because of childbearing at the time). She comes to the emergency department complaining of a 2-day history of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. The physical examination revealed bilateral crackles and a pansystolic murmur heard across the precordium. An urgent transthoracic echocardiography was obtained, and it revealed diffuse thickening and reduced mobility of the bioprosthesis. Which of the following is the most likely diagnosis and the most common bioprosthetic valve-related complication leading to reoperation?

- A. Paravalvular leak
- B. Structural valve degeneration
- C. Endocarditis
- D. Pannus formation
- E. Thrombus formation

52-9. The patient described in Question 52-8 asks whether she should have chosen a mechanical prosthesis at the time of her index surgery (and accepted the risks associated with anticoagulation and childbearing). In counseling her, which of the following statements is *true* regarding the expected long-term risk of reoperation after a mitral valve replacement surgery?

- A. The risk is higher with aortic valve replacement than with mitral valve replacement
- B. The risk is higher with younger patients
- C. The risk is higher with mechanical prostheses than with bioprostheses
- D. There is a higher short-term risk with mechanical prostheses but no difference in long-term risk
- E. The risk is negligible short- and long-term with newer-generation prosthetic valves

52-10. After initial medical management and discussions with the patient and the heart team, the decision was made to offer reoperative valve replacement to the patient described in Question 52-9. Which of the following may be helpful in preparation for the redo procedure?

- A. Transesophageal echocardiography
- B. Cardiac catheterization
- C. Noncontrast chest CT
- D. Prior operative reports
- E. All of the above

ANSWERS

- 52-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 52*) At 6 to 12 weeks after surgery, a complete evaluation including clinical history and examination, 12-lead ECG, and transthoracic echocardiography should be performed to assess functional status, blood pressure and rhythm, ventricular function, prosthetic valve function, gradients, and any paravalvular regurgitation, and anticoagulation adherence should be reviewed. Consensus guidelines recommend annual and symptom-triggered follow-up by a cardiologist for life, with the aim of detecting prosthesis dysfunction and the progression of other valvular heart disease. Follow-up solely by a family physician or as needed is not sufficient (options A, B, C, D).
- 52-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 52*) Transthoracic echocardiography should be performed annually after the fifth year postoperatively in patients with bioprosthetic valves; earlier in young patients who are at higher risk of accelerated valve dysfunction; and in any patient with a prosthetic valve if any new symptoms occur or there is clinical suspicion of complications based on clinical examination.
- 52-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 52*) The risk of infectious endocarditis is significantly higher in patients with prosthetic heart valves, but there is insufficient evidence available (1) to define the threshold for and type of prophylaxis required to minimize this risk and (2) to define the incremental risk posed to by adverse outcomes related to antibiotic use, including anaphylaxis and antibiotic resistance.^{1,2} Current consensus guidelines recommend antibiotic prophylaxis prior to dental procedures that involve manipulation of gingiva or apical tissue, or breach of the oral mucosa.
- 52-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 52*) Routine antibiotic prophylaxis is not recommended for patients with prosthetic valves who undergo genitourinary procedures, gastroscopy, colonoscopy, bronchoscopy, transesophageal echocardiography, vaginal or caesarian delivery, or skin or soft-tissue procedures, unless the patient has an active infection or is immunocompromised.^{1,2}
- 52-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 52*) The causes of prosthetic valve stenosis include bioprosthetic valve dysfunction, valve thrombosis, endocarditis with large burden of vegetation, and ingrowth of fibrous tissue (pannus).³
- 52-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 52*) Patient-prosthesis mismatch has been associated with decreased cardiac index, reduced functional improvement, less left ventricular mass regression, worse survival, and more adverse events in long-term follow-up. However, there are several confounding variables associated with a smaller indexed effective orifice area and with worse postoperative outcomes, including advanced age, female gender, and obesity; it is unclear to what extent these confounding variables contribute to the worse outcomes observed in patients with patient-prosthesis mismatch.⁴ Stroke is not typically associated with patient-prosthesis mismatch because this is an insidious hemodynamic issue.
- 52-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 52*) The reasons for anticoagulation nonadherence may include comorbidities and associated side effects, patient preference, socioeconomic barriers, and childbearing. Pregnancy in the first trimester is a contraindication to warfarin therapy. In an analysis of Medicaid patients, age less than 55 years was one of the strongest independent predictors of nonadherence to an anticoagulation regimen.⁵ This study also identified inadequate housing and care support, mental illness, and substance abuse as significant barriers to patient adherence with anticoagulation.
- 52-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 52*) Bioprosthetic structural valve degeneration is defined as any change in function of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. Structural valve degeneration is the most common valve-related complication in bioprosthetic valves.⁶ It occurs more rapidly in younger patients than in older patients, and earlier in the mitral position compared to the aortic position. Paravalvular leak is common but generally mild, and it infrequently leads to reoperation (option A). Endocarditis is not likely in this case due to the absence of constitutional symptoms or oscillatory mass seen on echo (option C). Pannus and thrombus formation are not suggested by the echo findings (options D and E).
- 52-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 52*) The risk of reoperation to replace a mechanical or bioprosthetic valve is similar over the first few years (option D), but the risk of having to replace a bioprosthesis after 8 to 12 years is higher (option C) as a result of an increasing incidence of structural valve dysfunction, which is the most common indication for reoperation on bioprostheses.⁷⁻¹² Structural valve dysfunction occurs more rapidly in younger patients than in older patients (option B), and earlier in the mitral position compared to the aortic position (option A). Although newer-generation valves have enhanced durability, structural valve dysfunction remains a nonnegligible risk (option E).
- 52-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 52*) Investigation of the patient requiring reoperative valve replacement should include transesophageal echocardiography to assess native and prosthetic valve function, to evaluate the presence and extent of endocarditis, thrombus, and pannus, and to determine cardiac function, including the presence

of pulmonary hypertension and right ventricular dysfunction.^{13,14} Cardiac catheterization should be performed to document native coronary artery anatomy, the presence and patency of coronary bypass grafts, and hemodynamics, including pulmonary artery pressures, cardiac output, and transvalvular gradients. Noncontrast chest CT is helpful to plan sternal reentry, which may be complicated by inadvertent division of structures adherent to the sternum, including the right ventricle, pulmonary artery, aorta, innominate vein, and patent bypass grafts. Prior operative reports are useful to confirm the size and type of previous prosthesis, location of bypass grafts, and technical challenges encountered at first surgery, which may affect the conduct of reoperation.

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CHAPTER 53

Antithrombotic Therapy for Valvular Heart Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 53-1.** A 62-year-old man with a prior history of idiopathic dilated cardiomyopathy was admitted to the cardiology unit with advanced heart failure and severe functional mitral regurgitation. During his admission, the patient suffered from recurrent pulmonary edema complicated by intractable hemodynamic instability. After discussing the case with the heart team, the patient underwent percutaneous edge-to-edge repair for mitral regurgitation using the MitraClip device. Which of the following antithrombotic regimens would you recommend to reduce this patient's risk of thromboembolic events post-procedure?
- A. Warfarin indefinitely
 - B. Apixaban indefinitely
 - C. Aspirin for 6 months along with clopidogrel for 30 days
 - D. Warfarin indefinitely along with aspirin for 6 months
 - E. No specific antithrombotic therapy is recommended
- 53-2.** A 75-year-old woman with a prior history of rheumatic heart disease and stage 5 chronic kidney disease presented to the emergency department following a fall complicated by a femoral neck fracture. She denied any history of falls prior to this event, and she had been generally very active and well. Her physical examination revealed an irregularly irregular pulse and a metallic click best heard at the apex. After reviewing her old medical notes, you noticed that the patient underwent a successful mechanical mitral valve replacement (MVR) surgery 15 years ago for which she was taking warfarin. The patient was subsequently evaluated by the orthopedic team, and the plan was to proceed with hip arthroplasty surgery. Which of the following antithrombotic regimens would you recommend during the perioperative period?
- A. Stop warfarin 2 to 4 days before surgery, start intravenous unfractionated heparin when the INR falls to < 2.0 , and restart warfarin 12 to 24 hours after surgery if bleeding risk allows
 - B. Stop warfarin 2 to 4 days before surgery, start low molecular weight heparin when the INR falls to < 2.0 , and restart warfarin 12 to 24 hours after surgery if bleeding risk allows
 - C. Stop warfarin 2 to 4 days before surgery and restart warfarin 12 to 24 hours after surgery if bleeding risk allows
 - D. Do *not* stop warfarin (maintain therapeutic INR), and proceed with hip surgery because the patient's risk for thromboembolic events is very high
 - E. Cancel the hip surgery and manage the patient conservatively
- 53-3.** A 55-year-old man with a prior history of mechanical MVR, hypertension, and dyslipidemia was admitted to the cardiac unit for a NSTEMI in the anterior territory. The patient underwent coronary angiography, and a drug-eluting stent was deployed in the proximal left anterior descending artery. The patient was discharged on triple therapy with warfarin, aspirin, and clopidogrel. Twelve months later, the patient returned to your clinic as part of follow-up and stated that he had been feeling very well since discharge and denied any cardiovascular symptoms or bleeding events. Which of the following antithrombotic regimens would you recommend at this time?
- A. Warfarin only
 - B. Apixaban only
 - C. Aspirin and clopidogrel
 - D. Warfarin and clopidogrel
 - E. Apixaban and aspirin
- 53-4.** You receive a phone call for an urgent consultation regarding a 31-year-old pregnant woman who was recently found to be pregnant. The patient had a mechanical mitral valve prosthesis implanted 5 years ago and was taking warfarin with a therapeutic INR up to this time. Which of the following anticoagulation regimens would *not* be an acceptable option for this patient?

- A. Warfarin for the first 36 weeks with a switch to heparin
- B. Low molecular weight heparin restricted to the first 6 to 12 weeks, followed by warfarin up to 36 weeks, with a switch to heparin
- C. Intravenous unfractionated heparin restricted to the first 6 to 12 weeks, followed by warfarin up to 36 weeks, with a switch to heparin
- D. Warfarin restricted to the first 6 to 12 weeks, followed by low molecular weight heparin up to 36 weeks, with a switch to heparin
- E. Unfractionated or low molecular weight heparin throughout the pregnancy

53-5. After extensive discussion with the patient described in Question 53-4, since she had an older-generation mechanical mitral valve prosthesis and was taking only 4 mg/d of warfarin, the decision was to continue warfarin throughout the pregnancy (up to 36 weeks). The patient, who is now in her second trimester, had been taking warfarin with an INR of 2.8 and a time in the therapeutic range of 80%. You receive a phone call from her perinatologist seeking advice on the best anticoagulation management at this stage. Which of the following recommendations would be appropriate for the management of this patient?

- A. Weekly INR with 2.0 to 3.0 target
- B. Weekly INR with 2.5 to 3.5 target
- C. Add aspirin and weekly INR with 2.0 to 3.0 target
- D. Add aspirin and weekly INR with 2.5 to 3.5 target
- E. Add aspirin and weekly INR with 3.0 to 4.0 target

53-6. A 64-year-old man with a prior history of a mechanical aortic valve replacement surgery presented to the emergency department complaining of acute dyspnea. The physical examination revealed a BP of 90/55 mm Hg, bilateral pulmonary crackles, and a harsh 5/6 systolic murmur over the aortic area; the aortic click was not audible. Upon reviewing the patient's old chart, he had been noted to have a softer 2/6 systolic murmur and audible aortic click since his valve replacement surgery. A chest x-ray confirmed the presence of florid alveolar edema and showed a well-positioned mechanical aortic valve prosthesis. The patient was intubated and underwent an urgent transesophageal echocardiogram, which revealed a large thrombus on the aortic valve prosthesis, associated with significant outflow obstruction. Which of the following is the most appropriate next step?

- A. Emergency surgery
- B. Admission to the cardiovascular ICU for stabilization and surgery in 2 to 3 days
- C. Intravenous unfractionated heparin with half-dose fibrinolysis
- D. Intravenous unfractionated heparin with fibrinolysis in 1 hour if the patient deteriorates
- E. Low molecular weight heparin without fibrinolysis

53-7. You receive a phone call from a family physician seeking advice on the best anticoagulation regimen for 64-year-old woman with a prior history of a mechanical MVR 15 years ago. A couple of years ago, aspirin (81 mg) was added to warfarin by the family physician for a suspected diagnosis of stable angina. Which of the following antithrombotic regimens would you recommend at this time?

- A. Stop aspirin and continue with warfarin alone
- B. Continue with the current regimen (warfarin and aspirin)
- C. Switch warfarin to apixaban and stop aspirin
- D. Switch warfarin to apixaban and continue aspirin
- E. Increase the dose of aspirin to 320 mg daily

53-8. A 27-year-old woman at 36 weeks' gestation, with no significant prior medical history, was admitted to the acute antenatal care unit with symptoms suggestive of acute decompensated heart failure. Upon further questioning, the patient stated that she had had a febrile illness a couple of weeks ago and since then had been feeling generally unwell. An echocardiography was obtained and revealed a myxomatous mitral valve with a mobile vegetation complicated by severe mitral regurgitation. The patient was stabilized on medical therapy and underwent an induced delivery. A few weeks after delivery, the patient experienced recurrent heart failure symptoms and underwent MVR with a bioprosthetic valve, in view of her wishes for future pregnancies. Which of the following antithrombotic regimens would you recommend during the first 3 months after MVR?

- A. Warfarin with a target INR between 2.0 and 3.0
- B. Warfarin with a target INR between 2.5 and 3.5
- C. Warfarin with a target INR between 3.0 and 4.0
- D. Apixaban alone
- E. Clopidogrel and aspirin

53-9. The patient described in Question 53-8 returned to your clinic 3 months after her bioprosthetic MVR as part of the routine follow-up. Which of the following antithrombotic regimens would you recommend at this time?

- A. Stop warfarin
- B. Continue warfarin

- C. Continue warfarin and prescribe low-dose aspirin
- D. Stop warfarin and prescribe low-dose aspirin
- E. Switch warfarin to apixaban

- 53-10.** An 85-year-old man with a past medical history of coronary artery disease, arterial hypertension, dyslipidemia, type 2 diabetes mellitus, and severe COPD was diagnosed with severe symptomatic aortic valve stenosis following admission to the cardiology ward with heart failure. Based on his predicted risk of operative mortality, the patient was deemed high risk for surgical aortic valve replacement and underwent transcatheter aortic valve replacement (TAVR). Which of the following antithrombotic regimens would you recommend after TAVR?
- A. Warfarin for the first 3 months followed by aspirin indefinitely
 - B. Aspirin only
 - C. Clopidogrel for the first 6 months along with lifelong low-dose aspirin
 - D. Clopidogrel for the first 6 months along with lifelong high-dose aspirin
 - E. Clopidogrel for the first 12 months along with lifelong low-dose aspirin

ANSWERS

- 53-1. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 53*) Following percutaneous edge-to-edge repair for mitral regurgitation using the MitraClip device, aspirin (325 mg/d) is recommended for 6 months along with clopidogrel (75 mg/d) for 30 days after the procedure.¹
- 53-2. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 53*) For patients with a mechanical mitral valve, bridging anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin is recommended to reduce the risk of adverse effects.² Warfarin is stopped 2 to 4 days before surgery. When the INR falls to < 2.0, intravenous heparin infusion or weight-adjusted low molecular weight heparin (twice daily) is initiated. This is stopped 4 to 6 hours (for unfractionated heparin) or 12 hours (for low molecular weight heparin) before surgery. Once bleeding risk allows (usually 12 to 24 hours after surgery), warfarin is restarted. The use of low molecular weight heparin is contraindicated in those with severe renal failure, as in this case (option B).
- 53-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 53*) After 12 months, stable coronary patients may be managed with oral anticoagulants alone. But in the case of mechanical valves, the addition of low-dose aspirin to anticoagulant therapy has been shown to be beneficial in the long term and is recommended. In select cases such as left main stenting, proximal bifurcation stenting, or proximal LAD stenting, clopidogrel 75 mg/d may be preferred over low-dose aspirin for the long-term treatment.
- 53-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 53*) Pregnancy with a mechanical heart valve constitutes the WHO risk class III (significantly increased risk of maternal mortality or severe morbidity).³ There is no ideal anticoagulation regimen. Anticoagulation options are (1) VKA (warfarin) throughout pregnancy with a switch to heparin at 36 weeks; (2) unfractionated or low molecular weight heparin restricted to the first 6 to 12 weeks, followed by warfarin up to 36 weeks, with a switch to heparin; and (3) unfractionated or low molecular weight heparin throughout the pregnancy.²⁻⁵ Warfarin is more efficacious than heparin for thromboprophylaxis, but it is associated with an increased risk of embryopathy, particularly between weeks 6 and 12 of gestation.⁶ Warfarin therapy throughout pregnancy is recommended for patients with a daily dose requirement of < 5 mg/d and for those who are at very high risk of thromboembolism (older generation mitral valve prosthesis or those with previous history of thromboembolism).²
- 53-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 53*) Current guidelines recommend frequent monitoring of anticoagulation therapy during pregnancy irrespective of the antithrombotic regimen chosen.^{2,3,5} INR should be measured weekly. For mechanical MVR, older-generation AVR, and those with risk factors for thromboembolism, the target INR should be 3 (range 2.5 to 3.5). For patients with a bileaflet aortic valve and no risk factors for thromboembolism, the recommended target INR is 2.5 (range 2 to 3). Low-dose aspirin (75 to 100 mg/d) is recommended for pregnant patients with either mechanical or bioprosthetic valves in the second and third trimesters.
- 53-6. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 53*) The ACC/AHA valvular heart disease guidelines recommend emergency surgery (class 1 recommendation) for left-sided prosthetic heart valve thrombosis with moderate to severe (NYHA 3-4) symptoms. Emergency surgery is also preferred in patients with a mobile or large thrombus (> 0.8 cm²). For patients with mild symptoms (NYHA 1 to 2) of recent onset (< 14 d) and small thrombus burden (< 0.8 cm²), an initial trial with intravenous infusion of unfractionated heparin may be given. If this is unsuccessful, fibrinolytic therapy is recommended.
- 53-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 53*) A systematic review found that adjunctive therapy with aspirin in addition to oral anticoagulation was associated with a reduction in overall mortality and thromboembolic

events among patients with mechanical heart valves at the cost of increased bleeding.⁷ This increased risk of bleeding was not seen among low-dose aspirin trials (aspirin 100 mg/d) (OR: 0.96, 95% CI: 0.60 to 1.55, $P = 0.87$). On the other hand, the effectiveness of low-dose aspirin (100 mg/d) was similar to that of higher-dose aspirin. Accordingly, the addition of low-dose aspirin (< 100 mg) is recommended by the American College of Cardiology and the American Heart Association for all patients with mechanical valves.² The newer oral anticoagulants (dabigatran, apixaban, rivaroxaban) are not indicated for atrial fibrillation associated with rheumatic MS, mechanical or bioprosthetic heart valve, or after mitral valve repair.^{2,8}

- 53-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 53*) Thromboembolic risk associated with bioprosthetic valves appears to be greatest in the first 3 months after implantation.⁹ The risk is greater after mitral valve surgery. Based on this risk, antithrombotic therapy with a vitamin K antagonist is recommended for the first 3 months after bioprosthetic MVR to achieve an INR of 2.5 (range 2.0 to 3.0).^{2,10}
- 53-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 53*) After 3 months, the tissue valve and the repaired valve can be treated as native valve and anticoagulation discontinued. After the first 3 months, low-dose aspirin (75 to 100 mg/d), should be continued indefinitely for bioprosthetic AVR or MVR and mitral valve repair patients² because this is associated with a reduction in thromboembolic events compared with no antithrombotic treatment.¹¹
- 53-10. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 53*) For patients undergoing TAVR, clopidogrel 75 mg daily is recommended for the first 6 months after the procedure, along with lifelong low-dose aspirin (75 to 100 mg daily).²

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CHAPTER 54

Management of Mixed Valvular Heart Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 54-1.** The general rule for treating secondary tricuspid regurgitation (TR) is to optimize therapy for the underlying cause. Which of the following TR outcomes may be observed after correction of underlying mitral or aortic valve disease?
- A. Improvement of TR
 - B. Worsening of TR
 - C. No change in TR
 - D. De novo TR
 - E. All of the above
- 54-2.** Most TR is secondary to overload caused by left-sided heart disease or by lung disease. Which of the following statements about tricuspid intervention during left-sided surgery is *true*?
- A. TR surgery reduces postoperative TR but not RV dilatation
 - B. TR surgery reduces mortality in this setting
 - C. TR surgery reduces the risk of postoperative conduction abnormalities
 - D. 10-year survival is similar for mechanical prostheses versus bioprostheses
 - E. All of the above
- 54-3.** A 62-year-old man with a history of mitral valve replacement (MVR) 2 years ago presents with increasing leg edema and abdominal girth. A holosystolic murmur is heard at the lower sternal border, with large visible “v” waves noted in the jugular venous pulsation. Echocardiography reveals a normally functioning mitral bioprosthesis, but there is severe functional TR, which was preoperatively graded as mild-to-moderate TR. Which of the following factors may contribute to the variable response of the TR after correction of the mitral valve disease?
- A. Right ventricular size and function
 - B. Pulmonary arterial hemodynamics
 - C. The underlying etiology of the left-sided valve disease
 - D. Atrial fibrillation
 - E. All of the above
- 54-4.** A meta-analysis reviewed the fate of moderate-to-severe MR in a large pool of patients having undergone transcatheter aortic valve replacement (TAVR).¹⁶ In what proportion of patients did the MR severity improve post-TAVR?
- A. 10%
 - B. 30%
 - C. 50%
 - D. 70%
 - E. 90%
- 54-5.** A 90-year-old woman with a history of TAVR 12 months ago presents for routine echocardiographic follow-up. She is feeling well, and her functional class has improved from NYHA III pre-TAVR to NYHA I at the present time. The echocardiogram reveals only trace MR, whereas it was graded as “at least moderate” before TAVR. Which of the following factors may contribute to the MR improvement after TAVR?
- A. Secondary MR etiology
 - B. Aortic mean gradient > 40 mm Hg
 - C. Sinus rhythm
 - D. None of the above

E. All of the above

54-6. Irrespective of etiology, it is unusual for mixed aortic valve disease to have equal components of aortic stenosis (AS) and regurgitation (AR). Which of the following statements is *true*?

- A. In cases of moderate combined AS/AR, the AS pressure gradients should be lower than expected for isolated moderate AS
- B. In cases of moderate combined AS/AR, the LV behaves much more as it would in pure AR
- C. In cases of moderate combined AS/AR, outcomes resemble those of AR
- D. None of the above
- E. All of the above

54-7. Which of the following statements about mixed aortic valve disease, particularly moderate combined AS/AR, is *true*?

- A. The outcome compares best with that of severe AS
- B. The outcome is substantially worse than moderate AS
- C. The outcome is substantially worse than moderate AR
- D. Aortic valve replacement should be performed at symptom onset
- E. All of the above

54-8. A 51-year-old woman with a prior history of diet-controlled type 2 diabetes and COPD was referred by her GP to the cardiology clinic because of a heart murmur. She was very active and reported no cardiovascular symptoms. A physical examination revealed “a mixed murmur” as described by the examiner. A transthoracic echocardiogram revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and an MVA of 1.1 cm^2 . In addition, there was moderate aortic regurgitation, a left ventricular ejection fraction (LVEF) of 65%, and a left ventricular end systolic dimension of 37 mm. Which of the following statements about the combination of MS and AR is *true*?

- A. It is seen almost always in the setting of senile degenerative calcific valvular disease
- B. It may lead to underestimation of AR severity during physical examination but not during imaging
- C. It may lead to underestimation of AR severity during imaging but not during physical examination
- D. It may lead to underestimation of AR severity both during physical examination and during imaging.
- E. None of the above

54-9. A 53-year-old woman with no prior medical history was referred for cardiology consultation for a 6-month history of dyspnea on exertion. A physical examination revealed a soft systolic murmur best heard at the apex. A transthoracic echocardiogram revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, an MVA of 1.8 cm^2 , and a diastolic pressure half time of 130 ms. In addition, there was significant MR, LVEF of 66%, and LVESD of 35 mm. Which of the following is the best next step in the management of this patient?

- A. Immediate admission for IV vasodilators
- B. Invasive hemodynamics
- C. Elective mitral valve repair
- D. Elective mitral valve replacement
- E. Elective balloon mitral valvotomy (BMV)

54-10. A 50-year-old woman with a prior history of acute rheumatic fever at the age of 11 was referred for cardiology consultation for a 3-month history of dyspnea on minimal exercise. Physical examination revealed a loud first heart sound and a middiastolic rumble. A transthoracic echocardiogram was performed and revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, an MVA of 0.9 cm^2 , and a diastolic pressure half time of 230 ms. In addition, there was moderate MR, LVEF of 62%, and LVESD of 39 mm. Which of the following is the best next step in the management of this patient?

- A. IV vasodilators
- B. IV beta-blockers
- C. Invasive hemodynamics
- D. MVR
- E. BMV

ANSWERS

54-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 54*) Although it has long been hoped that correction of the hemodynamic load associated with underlying mitral or aortic valve disease would improve secondary TR, observed results remain unpredictable, with TR sometimes improving (option A), sometimes worsening (option B), sometimes

remaining unchanged (option C), and sometimes even arising de novo following left-sided valve surgery (option D).¹⁻⁶ All of the options are thus possible TR outcomes after correction of underlying mitral or aortic valve disease. Therefore the best answer is option E.

- 54-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 54*) It seems clear that tricuspid intervention during left-sided surgery reduces postoperative TR and RV dilatation (option A is thus not correct). However, it has been difficult to show that TR surgery reduces mortality (option B is thus not correct).^{5,7-14} Although tricuspid repair reduces postoperative heart failure and TR, it has increased the risk of postoperative conduction abnormalities (option C is thus not correct), requiring permanent pacemaker implantation in some but not all reports. In a large meta-analysis, 10-year survival (about 60%) was nearly identical for bioprostheses versus mechanical prostheses, and this is the correct answer (option D).¹⁵
- 54-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 54*) The variable response of TR to correction of left-sided valve disease is in part related to the causes and effects of the left-sided valve disease and its correction. Predictors of TR progression after left-sided valve surgery include: advanced age, right ventricular dilation and dysfunction (option A), tricuspid annular dilation, persistent pulmonary hypertension after surgery (option B), rheumatic or ischemic mitral valve disease etiology (option C), and atrial fibrillation (option D). All of the options are correct, and therefore the best answer is option E.
- 54-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 54*) In high-risk AS patients, the presence of MR must be considered in the decision of SAVR versus TAVR because the MR is not addressed directly at the time of TAVR but can be repaired at the time of SAVR. Thus it would be important to be able to predict the fate of MR following TAVR in making AVR decisions. In a meta-analysis of observational and randomized studies,¹⁶ MR severity improved in 50% of patients over a median follow-up of 180 days after TAVR. Other studies have shown variable results.¹⁷⁻²⁹ Options A, B, D, and E are therefore not correct.
- 54-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 54*) Although the outcome of MR following TAVR still remains difficult to predict, Toggweiler and coworkers²⁴ found that MR was more likely to improve when it was secondary (option A), when there was an aortic mean gradient > 40 mm Hg (option B), and when atrial fibrillation was absent (eg, sinus rhythm, option C). All of the options are correct, and therefore the best answer is option E.
- 54-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 54*) In cases of moderate combined AS/AR, the LV behaves much more as it would in pure AS rather than in AR (option B is thus not correct), and outcomes resemble those of AS (option C is thus not correct).³⁰ Aortic regurgitation causes increased systolic flow through the moderately stenotic valve, thereby increasing jet velocity, pressure gradient, and in tandem, pressure overload on the LV (option A is thus not correct). In turn, the patient and his or her LV respond primarily to the pressure overloads. All of the options are incorrect, and therefore the best answer is option D.
- 54-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 54*) The outcome for moderate combined AS/AR compares best with that of severe AS (option A), and substantially worse than moderate AS or moderate AR (options B and C).³¹ Thus the management of mixed AS/AR should follow the guideline strategy for managing patients with pure AS. Aortic valve replacement should be performed at symptom onset (option D) and might be considered for patients with jet velocity exceeding 5 m/s or patients with abnormal exercise tolerance tests. All of the options are correct, and therefore the best answer is option E.
- 54-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 54*) The combination of MS and AR is seen almost always in the setting of rheumatic heart disease (and not in the setting of senile degenerative calcific valvular disease—option A). It may be confusing, especially by understating the severity of AR.³² Because MS limits LV inflow, total LV volumes and the manifestations of volume overload for any degree of AR are lessened, potentially causing underestimation of AR severity both during physical examination and during imaging. Options B, C, and E are therefore not correct.
- 54-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 54*) Mixed mitral stenosis (MS) and mitral regurgitation (MR) usually occurs in the context of rheumatic heart disease. The management dilemma often presented to clinicians is whether the presence of symptoms in a patient with moderate MS and moderate MR is the result of the valve disease, because neither lesion by itself would probably cause symptoms. Further, if the valve is causing symptoms, current guidelines are unclear with respect to management. Thus although symptom onset in VHD is almost always a cause for mechanical intervention, moderate disease is not (options C, D, and E are therefore not correct). In such cases, invasive hemodynamics performed at rest or during exercise often clarifies the issue. If exercise generates filling pressures that are high enough to cause the patient's symptoms, it is highly likely that MS/MR is the cause of both the clinical and the hemodynamic consequences. This patient, with a history of exertional dyspnea and a moderate VHD, is relatively stable and therefore does not require immediate admission for IV vasodilators (option A).
- 54-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 54*) This patient is symptomatic, and symptom onset in VHD is almost always a cause for mechanical intervention. Therefore, there is no role for IV vasodilators (option A) and beta-blockers (option B) in this case. Although invasive hemodynamics may be considered in cases of discordance between the clinical presentation and the echo data, this would not be the best next step in the management of this symptomatic patient with severe MS (option C). Balloon mitral valvotomy (BMV) is usually contraindicated because it may worsen

MR (option E), and therefore MVR is indicated for relief of symptoms.

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SECTION 9

Congenital Heart Disease

CHAPTER 55

Mendelian Basis of Congenital and Other Cardiovascular Diseases

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 55-1.** A 54-year-old man presents to your office to establish care. His family history is notable for hypertrophic cardiomyopathy in his grandfather, paternal uncle, and sister. His father and his two other brothers are unaffected. He has previously undergone genetic testing and is a carrier for a mutation in the *MYH6* gene that is associated with hypertrophic cardiomyopathy. He is otherwise healthy and denies any functional limitation. His electrocardiogram and echocardiogram are essentially normal. Which of the following concepts explains your patient's lack of a phenotype?
- A. Low expressivity
 - B. Variable penetrance
 - C. Genetic heterogeneity
 - D. Spontaneous mutation to a wild type allele
 - E. The allele is recessive
- 55-2.** A 62-year-old woman presents to your office to establish care. Her past medical history is notable for aortic valve replacement with arch repair for a thoracic aortic aneurysm. Her exam is notable for short stature and low-set ears. She was unable to have children despite trying to become pregnant. Karyotype analysis would likely reveal which of the following?
- A. Trisomy 21
 - B. Trisomy 18
 - C. Trisomy 13
 - D. Monosomy of the X chromosome
 - E. A deletion in the long arm of chromosome 22
- 55-3.** A 45-year-old man presents to your office with exertional dyspnea and palpitations. His exam is notable for brown spots around his lips and eyes. His past medical history is notable for resection of a pituitary adenoma. His cardiac MRI is shown in [Figure 55-1](#). This patient likely has a mutation in which of the following genes?



FIGURE 55-1 Cardiac MRI for the patient in Question 55-3. (Case courtesy of A. Prof Frank Gaillard, Radiopaedia.org, rID: 8544)

- A. *JAG1*
- B. *TBX5*
- C. *NKX2.5*
- D. *PTPN11*
- E. *PRKRA1A*

55-4. You are asked to consult on a 45-year-old man admitted to the neurology service with a stroke. His past medical history includes hypertrophic cardiomyopathy and chronic kidney disease with proteinuria. His family history is notable for multiple family members on his maternal side with enlarged hearts, including his uncle and grandfather. His physical exam suggests normal filling pressures, no inducible obstruction, and right arm weakness. An ECG shows normal sinus rhythm with left ventricular hypertrophy, and an echocardiogram shows hyperdynamic ventricular function with concentric hypertrophy. Which of the following tests would be useful for diagnosing his underlying disorder?

- A. Genetic testing for sarcomeric mutations
- B. Measurement of α -Gal A levels
- C. Genetic testing for *PRKAG2* mutations
- D. Genetic testing for *FRDA* mutations
- E. A cardiac MRI to evaluate for iron overload

55-5. A 43-year-old woman presents to your clinic for a second opinion regarding her dilated cardiomyopathy. Outside records reveal an ejection fraction of 35% with left ventricular dilation. Clinically, she is well-compensated and on maximally tolerated guideline-directed therapy for her heart failure. Her course has been uncomplicated, and she has no history of arrhythmia. Her past medical history is otherwise unremarkable, but her family history is notable for multiple family members with a similar cardiomyopathy on her maternal side. In which of the following genes is she most likely to have a mutation?

- A. *TTN*
- B. *LMNA*
- C. *CRYAB*
- D. *DMD*
- E. *SCN5A*

55-6. A 17-year-old basketball player presents to your office for syncopal events. The events have been occurring more often over the past several months. Her exam is unremarkable. Her ECG is notable for an epsilon wave. Cardiac MRI shows a thin right ventricle with prominent fatty infiltration. Which of the following hereditary conditions is she most likely to have?

- A. Hypertrophic cardiomyopathy
- B. Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- C. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

- D. Emery–Dreifuss syndrome
- E. Brugada syndrome

55-7. A 25-year-old man from Thailand presents to your office for evaluation of recurrent syncopal episodes. The episodes have no prodrome. He has a family history of these episodes, with numerous family members on his paternal side having suffered sudden death, either as infants or as young adults. His ECG is shown in [Figure 55-2](#). A physical examination is unremarkable. In which of the following genes does he most likely have a mutation?

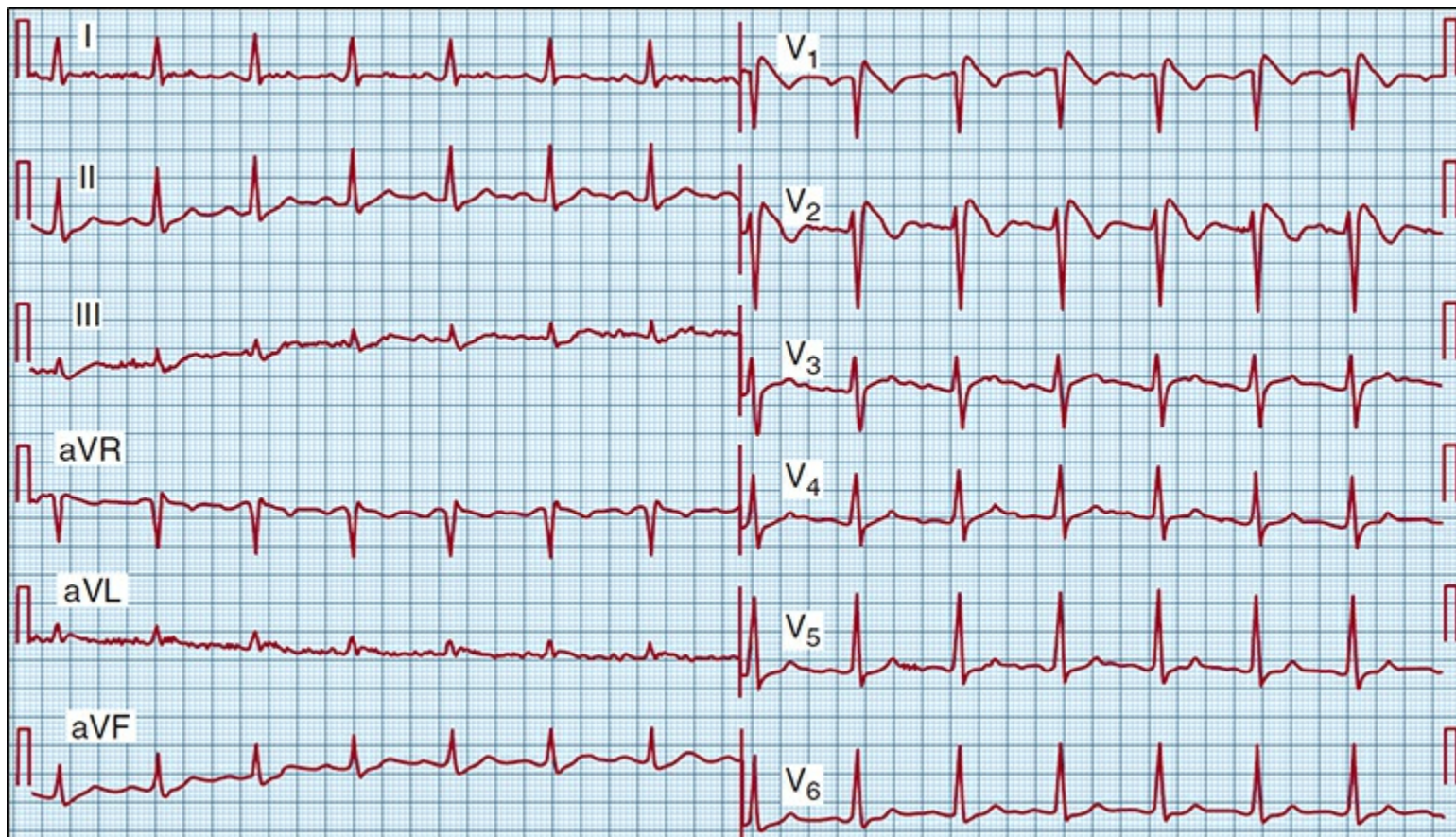


FIGURE 55-2 ECG for patient in Question 55-7.

- A. *KCNQ1*
- B. *KCNH2*
- C. *KCNJ2*
- D. *DSP*
- E. *SCN5A*

55-8. A 23-year-old woman is referred for evaluation after an abnormal lipid check at an employee health screening fair. Family history is notable for premature coronary artery disease on both sides of her family. She says that her family is known to have a mutation in a gene that affects cholesterol, but she cannot remember the name of the gene. Which of the following mutations is she *unlikely* to have?

- A. Loss of function mutations in *LDLR*
- B. A mutation of *APOB* that leads to a decreased affinity of APOB for the LDL receptor
- C. A mutation of *PSCK9* that causes increased clearance of the LDL receptor
- D. A mutation in the *LDLRAP1* that decreases LDL clearance
- E. A mutation in *ABCA1* that promotes free cholesterol transport to the extracellular space

55-9. Mutations to which of the following genes are *not* associated with primary pulmonary hypertension (PPH)?

- A. *BMPR2*
- B. *ACVRL1*
- C. *KCNA5*
- D. *FBN1*
- E. *KCNK3*

55-10. A 35-year-old man is referred to you for management of a thoracic aortic aneurysm. He has a family history of aortic aneurysms and is positive for a genetic mutation in the *FBN1* gene. Which of the following is *not* likely to be observed in this patient?

- A. Dislocated lens
- B. Aortic regurgitation
- C. Arachnodactyly
- D. Bifid uvula
- E. Mitral regurgitation

ANSWERS

- 55-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient carries a disease allele but does not have signs or symptoms of the disease, suggesting that the allele is not fully penetrant (option B). Expressivity refers to variable degrees of disease severity in carriers of the disease allele, but all carriers exhibit some signs of the disease (option A). Genetic heterogeneity refers to different disease alleles at different loci that can result in the same phenotypic disease (option C). For instance, multiple mutations in different genes can result in hypertrophic cardiomyopathy. The pattern of inheritance here is consistent with an autosomal dominant allele (option E). Like your patient, his father is likely to also carry the disease allele but not have phenotypic disease. This patient tested positive for the disease allele, so spontaneous mutation to a wild type allele is unlikely (option D).
- 55-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient has Turner syndrome, which is associated with monosomy of the X chromosome (option D). Patients with Turner syndrome can have a bicuspid aortic valve, often associated with aortic aneurysms.¹ Trisomy 21 is associated with Down syndrome (option A). Trisomy 18 is associated with Edwards syndrome (option B). Trisomy 13 is associated with Patau syndrome (option C). A deletion in the long arm of chromosome 22 is associated with DiGeorge syndrome (option E).
- 55-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient has Carney complex, manifested by the atrial myxoma shown in the cardiac MRI, lentigines, and endocrine tumors. The Carney complex is associated with mutations in *PRKRA1A* (option E). Mutations in *JAG1* are associated with Alagille syndrome (option A). Mutations in *PTPN11* are associated with Noonan syndrome (option D). Mutations of the cardiac transcription factors *NKX2.5* and *TBX5* are associated with VSDs and Holt–Oram syndrome, respectively (options B and C).
- 55-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient likely has Fabry's disease. Fabry's disease is an X-linked disorder (note that only males on his maternal side are affected) that involves the heart and kidneys. The diagnosis is established by measuring α -Gal A levels and activity in leukocytes (option B). Fabry's disease is associated with transient ischemic attacks and stroke. Fabry's disease is an example of one of the many disorders that can cause hypertrophic cardiomyopathy, such as glycogen storage diseases with *PRKAG2* mutations and Friedrich's ataxia with mutations in the *FRDA* locus (options C and D). Iron overload is seen in hemochromatosis, but this usually manifests as a dilated cardiomyopathy (option E). Sarcomeric gene mutations are associated with hypertrophic cardiomyopathy (option A).
- 55-5. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient has an isolated hereditary dilated cardiomyopathy. Up to 25% of these cardiomyopathies are associated with a mutation in the sarcomeric gene *TTN* (option A).² Cardiomyopathies involving sarcomeric genes tend to be isolated cardiomyopathies without other organ systems being involved. Mutations in *DMD* (option D) and *CRYAB* (option C), by contrast, are also associated with skeletal myopathies. Hereditary cardiomyopathies due to mutation in *LMNA* (option B) and *SCN5A* (option E) tend to be associated with arrhythmias.
- 55-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient most likely has ARVC with involvement of the right ventricle and fatty dysplasia of the right ventricle (option C). Hypertrophic cardiomyopathy would be noted by a thickened ventricle by cardiac MRI (option A). CPVT is marked by arrhythmias without structural changes to the right ventricle (option B). Emery-Dreifuss is due to a mutation in the *LMNA* gene that results in cardiac arrhythmia and depressed left ventricular function (option D). Brugada syndrome results in sudden death and cardiomyopathy (option E).
- 55-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 55*) This patient likely has Brugada syndrome. His ECG has a typical pattern with ST elevations in the right precordial leads. *KCNQ1*, *KCNH2*, *KCNJ2* are all related to long-QT syndromes (options A to C). Mutations in desmoplakin (*DSP*) are related to ARVC (option D). Mutations in *SCN5A* can cause Brugada syndrome, LQT3, and other conduction defects (option E).
- 55-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 55*) Monogenic syndromes that can lead to premature coronary atherosclerosis include familial hypercholesterolemia, fish eye disease, and Tangier disease. Mutations of the *LDLR*, *APOB*, *PSCK9*, and *LDLRAP1* all can result in familial hypercholesterolemia (options A through D). Mutations of *ABCA1* can cause Tangier disease, by reducing the efflux of free cholesterol to the extracellular space (option E).
- 55-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 55*) Primary pulmonary hypertension is a familial disease with an autosomal dominant mode of inheritance in 5% to 10% of the cases. PPH is a genetically heterogeneous disease. Mutations in bone morphogenic protein receptor type II (*BMPR2*), mapped to chromosome 2q31–33, are responsible for approximately 50% of the familial PPH and 10% to 15% of the sporadic cases (option A).^{3,4} Mutations in *ACVRL1*, which codes for a type I receptor of the TGF- β family, cause an autosomal-dominant vascular disorder characterized by pulmonary hypertension, hereditary hemorrhagic telangiectasia (HHT), and visceral arteriovenous malformations (option B).⁵ Likewise, mutations in *SMAD9*, *ENG* encoding endoglin, *CAV1* encoding caveolin 1, *KCNA5* and *KCNK3*, both encoding potassium channels, and *EIF2AK4*, coding for eukaryotic translation initiation factor 2 alpha kinase 4, are

causes of PPH (options C and E).⁶⁻⁸ Mutations in *FBN1* are associated with Marfan syndrome (option D).

55-10. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 55*) Marfan syndrome is associated with cardiovascular abnormalities, including aortic aneurysm and dissection, aortic regurgitation, and mitral regurgitation (options B and E). In addition to cardiovascular abnormalities, Marfanoid habitus (increased height, disproportionately long limbs and digits), lens dislocation or subluxation, arachnodactyly, thoracic abnormalities, and increased joint laxity are common clinical features (options A and C). Bifid uvula is a classic feature of Loeys–Dietz syndrome (option D).⁹

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CHAPTER 56

Congenital Heart Disease in Adolescents and Adults

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 56-1.** A 56-year-old man with a nonrestrictive VSD develops worsening exercise intolerance, pulmonary hypertension, and cyanosis. Which of the following is *not true* of the Eisenmenger syndrome?
- A. Survival in patients with Eisenmenger physiology is reduced compared to healthy control subjects
 - B. Patients with Eisenmenger physiology are susceptible to *in situ* pulmonary arterial thrombosis
 - C. The risk for hyperviscosity is low, with a hemoglobin < 20 g/dL
 - D. A pulmonary vasodilator may be indicated
 - E. Closure of the VSD is indicated
- 56-2.** Which of the following patients *does not* require prophylactic antibiotics prior to bacteremic procedures, such as dental surgery?
- A. A 54-year-old man with a mechanical mitral valve prosthesis
 - B. A 43-year-old woman with repaired patent ductus arteriosus
 - C. A 43-year-old woman with Eisenmenger complex
 - D. A 32-year-old man with tricuspid atresia treated with a Fontan conduit
 - E. A 31-year-old man with a history of infective endocarditis.
- 56-3.** A 31-year-old woman with a history of mechanical mitral valve replacement presents to your office for pregnancy counseling. She has excellent functional capacity. Echocardiography reveals normal ventricular function and a well-functioning mechanical mitral valve. Her medications are notable only for warfarin 3 mg daily. Her INR has been stable on this dose for the past several years. Which of the following would be appropriate advice?
- A. If she were to become pregnant, termination of the pregnancy would be recommended
 - B. She could continue with warfarin during the second and third trimesters of pregnancy
 - C. She should undergo caesarean section
 - D. She would have an increased risk for miscarriage
 - E. None of the above
- 56-4.** A 24-year-old woman presents to your office to establish care. She has a past medical history notable for atrial septal defect (ASD) but does *not* bring prior records. She denies any history of valvular disease. Her ECG shows RSR' and a rightward axis. She is physically fit and exercises regularly without limitation. She wants to know about her prognosis. Which of the following would you tell her?
- A. Pregnancy is contraindicated at this stage.
 - B. She most likely has a primum defect
 - C. Antimicrobial prophylaxis against endocarditis is recommended with dental procedures
 - D. She is potentially at risk for right ventricular (RV) failure, pulmonary hypertension, and tricuspid regurgitation over time
 - E. Systemic anticoagulation is indicated to prevent paradoxical emboli
- 56-5.** A 56-year-old man presents to your office for hypertension. On exam, you note a very loud holosystolic murmur at the lower sternal border. He exercises regularly without limitation. Echocardiography reveals a small restrictive perimembranous VSD and suggests normal pulmonary pressures. Which of the following is the next best step in management?
- A. Prophylactic closure
 - B. Recommendation for antimicrobial prophylaxis against endocarditis with invasive procedures
 - C. Continued observation
 - D. A and B

E. None of the above

56-6. A 48-year-old man presents to your office to establish care. He has a history of tetralogy of Fallot repaired with anterior ventriculotomy followed by VSD repair and a pericardial transannular patch. Over his lifetime, which of the following is this patient *not* at risk for?

- A. Ventricular arrhythmias
- B. Progressive pulmonary regurgitation
- C. Eisenmenger physiology
- D. A and B
- E. B and C

56-7. A 25-year-old with pulmonic stenosis presents to your clinic. She has excellent exercise capacity and is otherwise healthy. Routine echocardiography confirms pulmonic stenosis with dysplastic leaflets and no evidence for infundibular stenosis. The peak gradient across the valve is 45 mm Hg, and the mean gradient is 35 mm Hg. Which of the following would be the next best steps in her management?

- A. Continued surveillance
- B. Recommendations for endocarditis prophylaxis with bacteremic procedures
- C. Percutaneous balloon valvuloplasty
- D. Exercise stress testing
- E. C and D

56-8. A 42-year-old man presents for evaluation of shortness of breath and chest pain. Physical examination is notable for a harsh late peaking crescendo-decrescendo murmur at the upper sternal border that obscures S2. There is also an early diastolic decrescendo murmur at the mid-right sternal border. An echocardiogram reveals severe aortic stenosis, moderate aortic regurgitation, and a bicuspid aortic valve. Which of the following is also associated with the presence of a bicuspid aortic valve?

- A. Perimembranous VSD
- B. Parachute mitral valve
- C. Dilated ascending aorta
- D. Mitral stenosis
- E. None of the above

56-9. A 25-year-old man presents for evaluation of hypertension. A physical examination reveals a systolic blood pressure of the right arm of 180 mm Hg and a left lower leg systolic pressure of 150 mm Hg. Which of the following is *not true* of this patient's likely condition?

- A. He is at increased risk for intracranial aneurysms
- B. Correction of his lesion will cure his hypertension
- C. Even with treatment, he would be at risk for atherosclerotic heart disease, heart failure, and stroke
- D. He is at increased risk to have a bicuspid aortic valve
- E. None of the above

56-10. A 43-year-old woman presents to establish care. She has a history of isolated congenitally corrected transposition of the great arteries (TGA). Which of the following complications is she at increased risk for?

- A. Atrioventricular (AV) conduction disturbances
- B. Dysfunction of the systemic ventricle
- C. Aortic stenosis
- D. Aortic dissection
- E. A and B

ANSWERS

56-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 56*) This patient has the Eisenmenger complex (a reversed shunt in the presence of a nonrestrictive VSD). Survival in patients with Eisenmenger syndrome is reduced by approximately 20 years compared with healthy control subjects (option A).^{1,2} Shunt correction is contraindicated once shunt reversal occurs (option E). Cyanosis is associated with multiple complications, including *in situ* pulmonary arterial thrombosis, hyperviscosity (rarely with a hemoglobin < 20 g/dL), pulmonary arterial atherosclerosis, increased susceptibility to gout, and a heightened risk for infective endocarditis (options B and C).³⁻⁵ Promising advances have occurred over the past decade in the treatment of patients with pulmonary hypertension with pulmonary vasodilators. In the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) trial, patients with Eisenmenger

syndrome who were treated with Bosentan had a significant decrease in pulmonary vascular resistance and systemic vascular resistance, and a significant increase in 6-minute walk distance (option D).^{6,7}

- 56-2. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 56*) Certain subgroups are considered at higher risk for infective endocarditis. Guidelines from the European Society of Cardiology and the AHA/ACC on the prevention of infective endocarditis place patients with prosthetic valves, cyanosis, and systemic or pulmonary artery conduits, as well as patients with previous endocarditis, into a high-risk subgroup (options A, C, D, and E).^{8,9} Most other congenital cardiac conditions are in a moderate-risk category, except for patients who have undergone surgical or transcatheter repair of ASD, VSD, or PDA (without residua beyond 6 months), who are considered low risk provided there are no sequelae (eg, aortic valve prolapse, aortic regurgitation) (option B).
- 56-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 56*) Pregnancy results in considerable hemodynamic stress on the heart, and delivery is associated with large fluid shifts. Patients with left ventricular dysfunction, stenotic lesions, cyanotic heart disease, and aortic disease tend to have the highest risk for complications during pregnancy (options A and D). For most patients with cardiovascular disease, vaginal delivery is preferred because it results in less blood loss than caesarean section (option C). Pregnant women are inherently hypercoagulable, and their risk of valve thrombosis is increased, thus necessitating appropriate anticoagulation. Oral warfarin accomplishes this task well and is associated with a lower maternal risk, but it is teratogenic to fetuses, especially in the first trimester; the risk of teratogenicity is low after the eighth week of gestation.¹⁰ Therefore, warfarin is recommended by the ACC/AHA guidelines in the second and third trimesters of pregnancy (option B).¹¹
- 56-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 56*) Based on the presentation, this patient likely has a secundum ASD. The ECG usually demonstrates a characteristic RSR' complex in the anterior precordial leads with a rightward QRS axis in patients with secundum-type defects and left-axis deviation in those with primum-type ASD (option B). ASDs tend to be well tolerated initially, as in this patient. Thus, pregnancy is not contraindicated (option A). Progressive symptoms of dyspnea on exertion and palpitations often occur in adulthood and are caused by increasing right-sided chamber enlargement, pulmonary hypertension, RV failure, tricuspid regurgitation, and atrial arrhythmias (option D). Patients with large ASDs causing left-to-right shunts develop RV volume overload, which is relatively well tolerated for the first two decades. The risk of infective endocarditis is low unless the patient has coexistent valvular disease (eg, cleft mitral valve) (option C). Paradoxical emboli can occur but are rare, and preventive anticoagulation is not indicated (option E).
- 56-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 56*) This patient has a small restrictive VSD. For small restrictive defects or defects that have closed partially with time, the pulmonary vascular resistance is not significantly elevated, and the left-to-right shunt magnitude is mild (Qp:Qs ratio $\leq 1.5:1$). The intensity of the precordial holosystolic murmur is inversely related to the size of the defect; therefore, a disturbingly loud and harsh precordial holosystolic murmur in a patient with VSD should be viewed as a reassuring sign, not a cause for alarm. Although antibiotics for endocarditis prophylaxis are no longer recommended by the ACC/AHA guidelines, patients are at increased risk for endocarditis.¹¹ Small restrictive defects of the muscular or membranous septum may be watched conservatively without the need for operative intervention (option C).
- 56-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 56*) The four characteristic findings in TOF are (1) a malaligned VSD, (2) RV outflow or pulmonary valve or artery stenosis or atresia, (3) a dextraposed over-riding aorta, and (4) RV hypertrophy. Surgical treatment of tetralogy of Fallot is one of the major advances in cardiac surgery. The first generation of intracardiac repairs was performed via a large anterior ventriculotomy and often included incision of the pulmonary valve annulus and placement of a transannular patch made of pericardium or synthetic material. This technique successfully relieved the outflow tract obstruction but resulted in pulmonary valvular incompetence and severe pulmonary regurgitation. Over time, this can lead to RV failure (option B). Ventricular arrhythmias are more likely to occur following such repairs, and they often arise from the region of the transannular patch or ventriculotomy suture lines (option A). This patient has been repaired and no longer has shunting, so he is not at risk for Eisenmenger physiology (option C).
- 56-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 56*) Mild and moderate degrees of pulmonary stenosis (peak gradient ≤ 50 mm Hg) are well tolerated and generally do not require surgical or percutaneous intervention (option A).¹² Asymptomatic patients with severe pulmonary stenosis and a peak gradient ≥ 60 mm Hg or a mean gradient ≥ 40 should undergo intervention to reduce the severity of the stenosis. Symptomatic patients with a peak gradient ≥ 50 mm Hg or a mean gradient ≥ 30 mm Hg should undergo intervention (option C).¹³ Infective endocarditis of the pulmonary valve is rare; endocarditis prophylaxis during bacteremic procedures is not recommended (option B).¹³
- 56-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 56*) Options A, B, and D are associated with subvalvular aortic stenosis and the Shone complex. Patients with bicuspid aortic valves often have abnormalities of the aorta similar to patients with Marfan syndrome. The ascending aorta in patients with BAV gradually dilates at a mean of 0.9 mm/year (option C).¹⁴ The risk of dissection in patients with BAV is estimated to be five to nine times that of the general population and is highest in patients with concomitant coarctation.^{15,16} Patients with a BAV and ≥ 55 -mm aortic root diameter should be referred for surgical aortic root wrapping or replacement.¹¹

- 56-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 56*) This patient is likely to have coarctation of the aorta. A normal patient should have a 5- to 10-mm Hg increase in systolic blood pressure in the lower extremities compared with the upper extremities. Absence of this increase or the presence of a decrease in the lower extremities should arouse suspicion of coarctation. A BAV is present in about half of cases (option D). Intracranial aneurysms, often in the circle of Willis, have been detected in up to 10% of patients (option A).¹⁷ Patients with successfully treated coarctation often continue to have systemic arterial hypertension despite the absence of significant residual coarctation.^{18,19} Patients who undergo repair in childhood demonstrate very good long-term survival up to 60 years.²⁰ Late repair (> 14 years of age) is associated with higher rates of hypertension and decreased survival (option B).²¹ Patients with hypertension after late repair are at an increased risk of developing heart failure, atherosclerosis, stroke, and progressive aortic disease (option C).
- 56-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 56*) Congenitally corrected TGA is characterized by AV and ventriculoarterial discordance. From a circulatory oxygenation standpoint, these patients are “congenitally corrected,” essentially “two wrongs make a right,” and the pulmonary and systemic circulations run in series, not in parallel, as with dextro-TGA. There is ventricular inversion, and the respective AV valves follow the ventricles. Therefore, the systemic right ventricle (RV) is transposed to the left, and the tricuspid valve goes with it. The left atrium empties into the RV, which then pumps to the leftward and usually anterior aorta. Because the RV is the systemic ventricle, the RV is susceptible to failure over time (option B). The left ventricle (LV) and mitral valve are dextraposed, and the pulmonary artery emerges posteriorly from the LV. Fewer than 10% of patients are free of associated abnormalities, which include VSD (membranous or muscular) in up to 80%, pulmonic stenosis (valvular or subvalvular) in up to 70%, and tricuspid valve abnormalities (usually Ebstein anomaly) in 33% (options C and D).²² Furthermore, these patients have an increased incidence of AV conduction problems and complete heart block with age (option A).²³

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SECTION 10

Myocardial, Pericardial, and Endocardial Diseases

CHAPTER 57

Classification of Cardiomyopathies

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 57-1.** Which of the following is *true* about the American Heart Association (AHA) classification of cardiomyopathies?
- A. Primary cardiomyopathies are limited to cardiomyopathies with systolic dysfunction
 - B. Secondary cardiomyopathies are cardiomyopathies that are associated with a systemic, multiorgan disorder
 - C. A patient with hypertrophic cardiomyopathy (HCM) that results in a dilated phenotype would be considered to have a mixed cardiomyopathy
 - D. Ion channel disorders are *not* considered to be primary cardiomyopathies
 - E. None of the above
- 57-2.** Which of the following is *not true* of the 2008 European Society of Cardiology (ESC) classification of cardiomyopathy?
- A. Ion channelopathies are *not* included in the classification of cardiomyopathies
 - B. Familial cardiomyopathies are defined by the occurrence of a phenotype in more than one family member that could be caused by the same genetic mutation
 - C. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is considered a distinct cardiomyopathy, different from dilated cardiomyopathy, HCM, and restrictive cardiomyopathy
 - D. The genetic basis of cardiomyopathy is emphasized over morphofunctional features in the classification
 - E. None of the above are true
- 57-3.** Which of the following is *true* regarding the 2013 World Heart Foundation classification?
- A. The five attributes to determine classification include morphofunctional phenotype, organ system involvement, genetic pattern of inheritance, etiology, and stage
 - B. The classification system allows for specific genotypes to be annotated
 - C. Familial cardiomyopathy should be diagnosed when two or more family members are affected
 - D. Assessment of functional status incorporates the AHA staging system as well as the New York Heart Association (NYHA) classification system
 - E. All of the above are true
- 57-4.** A 47-year-old has HCM that progressed from the hypertrophic phenotype to the dilated phenotype. Under the MOGES classification, his M phenotype would be:
- A. M_H
 - B. M_D
 - C. M_{H+D}
 - D. M_R
 - E. None of the above
- 57-5.** The patient in Question 57-4 has an 8-year-old daughter. Genetic testing confirms she is also a carrier for the same sarcomeric mutation. A screening echocardiogram shows no structural abnormalities, and she is otherwise healthy. Which of the following is the best way to describe her morphofunctional description under the MOGES system?
- A. MOGES is *not* applicable since she does not have structural abnormalities
 - B. M_H
 - C. $M_{E[H]}$
 - D. $M_{0[H]}$
 - E. None of the above

- 57-6.** A 34-year-old man presents with 2 weeks of new-onset shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, and pedal edem. He is short of breath with moderate exertion. Prior to experiencing these symptoms, he had an upper respiratory tract illness. He has no family history for cardiomyopathy. Cardiac MRI shows a dilated left ventricle with an ejection fraction of 25%, and a scar pattern consistent with a viral myocarditis. Which of the following is the correct MOGES classification for this patient?
- $M_D O_{H+L} G_N E_V S_{C-II}$
 - $M_D O_H G_N E_V S_{C-II}$
 - $M_E O_{H+L} G_N E_V S_{C-II}$
 - $M_E O_{H+L} G_N E_V S_{B-II}$
 - $M_E O_H G_O E_V S_{B-II}$
- 57-7.** A 32-year-old woman transfers her care to you. She feels well and denies any cardiopulmonary limitation. She had been previously seen by a cardiologist and was assigned a MOGES classification of $M_0 O_0 G_{AD} E_{G-LMNA} S_{A-I}$. Which of the following is this patient at risk for?
- Arrhythmias
 - Stroke
 - Pulmonary hypertension
 - Respiratory failure
 - None of the above
- 57-8.** A 64-year-old man has a MOGES classification of $M_D O_0 G_{AD} E_{G-N} S_{D-IV}$. Which of the following is *true* about this patient?
- He has HCM
 - He has asymptomatic left ventricular dysfunction
 - He has a suspected genetic etiology, but the genetic defect is not known
 - He has a familial etiology that follows an autosomal recessive pattern of inheritance
 - None of the above
- 57-9.** What is the significance of the color code of MOGES classification?
- Asymptomatic carriers of a mutation
 - Known significance of a mutation
 - Morphofunctional phenotype
 - Functional status
 - None of the above
- 57-10.** A 37-year-old man has a MOGES classification of $M_D O_{Lu} G_N E_{AI-Sarcoid} S_{B-I}$. Which of the following is *true* about this patient?
- He has asymptomatic left ventricular dysfunction
 - He has a cardiomyopathy secondary to sarcoidosis
 - He has only cardiac involvement
 - A and B
 - None of the above

ANSWERS

- 57-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 57*) The AHA classification emphasizes the mechanism for cardiomyopathy, not the morphology.¹ Under the AHA classification, cardiomyopathies are not limited to disorders of systolic dysfunction (option A). Cardiomyopathies were divided into two major groups based on predominant organ involvement. The *primary* cardiomyopathies were those solely or predominantly confined to heart muscle. The primary cardiomyopathies were further categorized into genetic, acquired, and mixed varieties and represented the novelty of the AHA classification ([Figure 57-1](#)). Ion channel disorders are included as genetic cardiomyopathies ([Figure 57-1](#)) (option D). Thus, a patient with HCM would have a primary genetic cardiomyopathy (option C). The *secondary* cardiomyopathies showed pathologic myocardial involvement as part of systemic (multiorgan) disorders (option B).

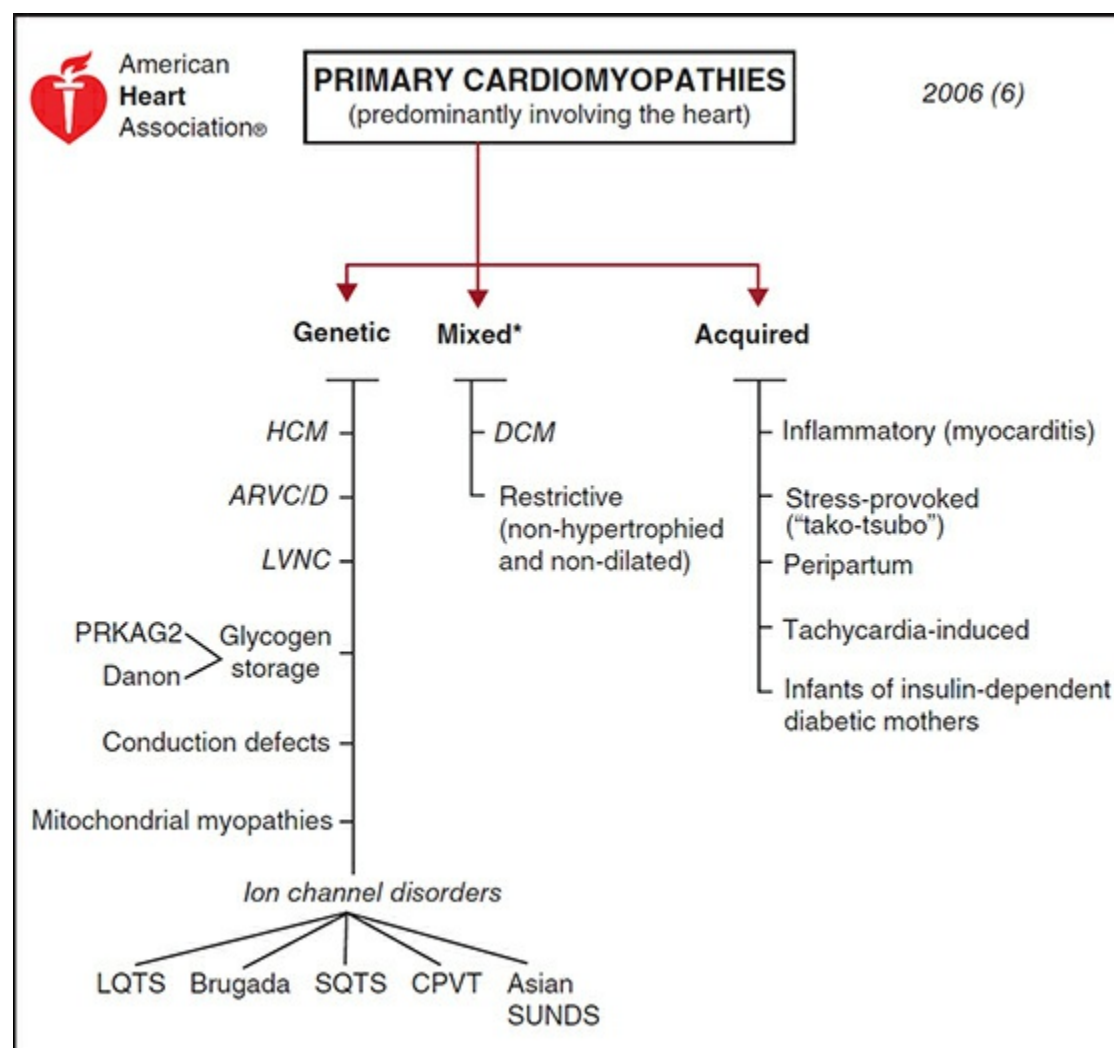


FIGURE 57-1 AHA classification of cardiomyopathy. (Reproduced with permission from Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention, *Circulation*. 2006 Apr 11;113(14):1807-1816.)

57-2. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 57*). The 2008 ESC classification of cardiomyopathy emphasizes morphofunctional features over the genetic features and thus differs from the AHA classification ([Figure 57-2](#)) (option D).² Morphofunctional categories include dilated cardiomyopathy, HCM, restrictive cardiomyopathy, ARVC, and idiopathic cardiomyopathy (option C). After morphofunctional classification, cardiomyopathies are classified as familial/genetic or nonfamilial/nongenetic. Familial cardiomyopathies are defined by the occurrence of a phenotype in more than one family member that could be caused by the same genetic mutation (option B). Ion channelopathies, a genetic subtype included in the AHA classification of primary cardiomyopathy, were not accepted as cardiomyopathy in the ESC classification because genes encoding for ion channels might not be associated with overt myocardial dysfunction (option A).

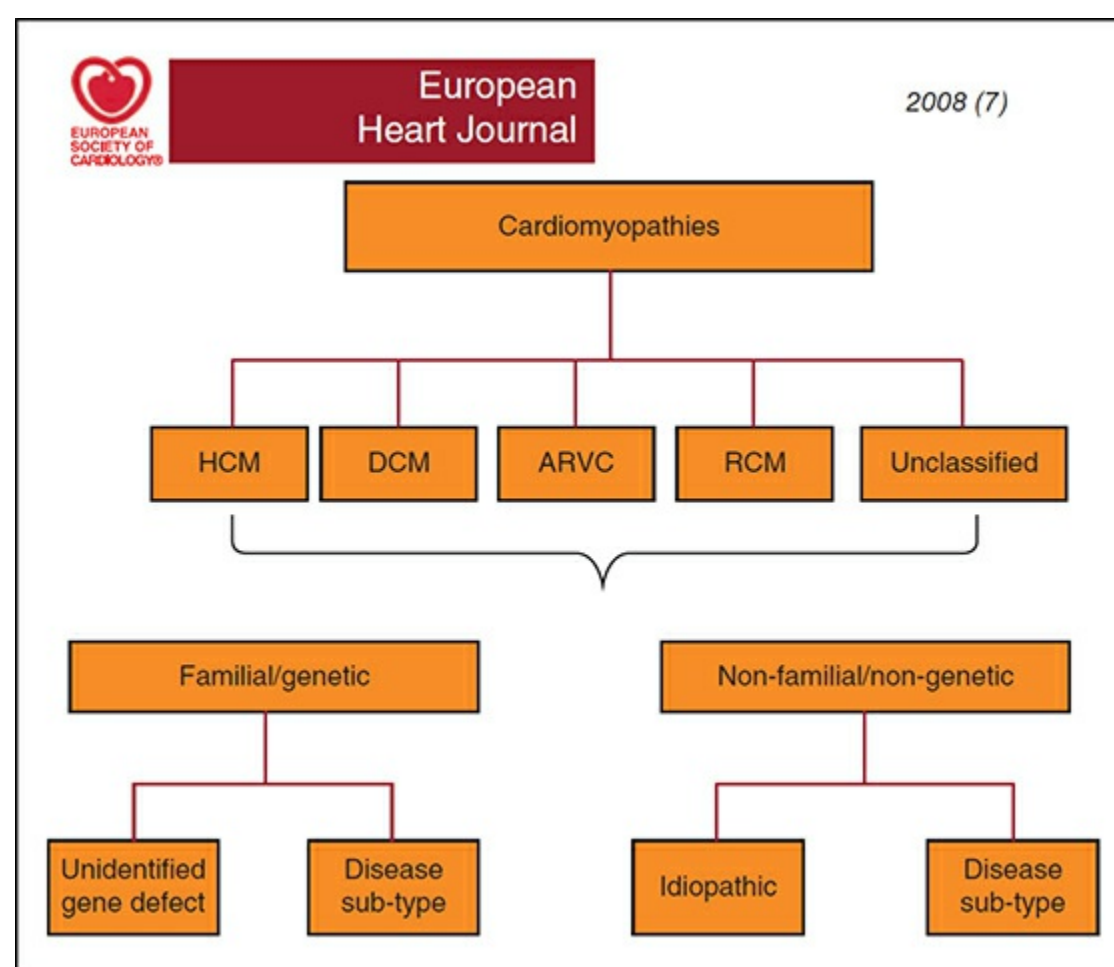


FIGURE 57-2 ESC classification of cardiomyopathy. (Reproduced with permission from Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on

- 57-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 57*). The WHF classification system builds on the AHA and ESC systems and is influenced by the TNM convention used in oncology.³ The five attributes used for classification include morphofunctional phenotype, organ system involvement, genetic pattern of inheritance, etiology, and stage (option A). The system is versatile and even allows for the annotation of specific mutations along with clinical relevant phenotypes such as ventricular morphology and functional status, using the AHA and NYHA staging conventions (options B and D).
- 57-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chapter 57*) Unlike previous classifications, the mixed or overlapping phenotypes can be easily presented in the MOGES classification system, such as HCM that evolves into dilated congestive phenotype (M_{H+D}) or HCM presenting with predominant restrictive pattern (M_{H+R}) (option C). Option A refers to a purely hypertrophic phenotype; option B refers to a purely dilated phenotype; and option D refers to a purely restrictive phenotype.
- 57-5. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 57*). Under the MOGES system, M allows the description of *early* phenotypes (M_E), such as when the diagnostic criteria for the suspected clinical phenotype (such as DCM or HCM) are not fulfilled and imaging data indicate an increased LV diameter and borderline LV function ($M_{E[D]}$) or possible LV hypertrophy ($M_{E[H]}$) (option C). Clinically healthy mutation carriers are described as $M_{0[H]}$ or $M_{0[D]}$ (0 is for zero) (options A and D). In this case, D and H refer to the phenotype of affected probands (option B).
- 57-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 57*). The MOGES classification system is provided in [Figure 57-3](#). He has a dilated cardiomyopathy, so he is M_D (options A, B). His organ involvement is the heart only, so he is O_H (options B and E). He has no family history and a history was taken, so he is G_N (options A through D). The etiology is likely viral, so he is E_v . Finally, he is stage C and has class II symptoms, indicated by S_{C-II} (options A through C).

SUBSCRIPT	M		O		G		E		S	
	MORPHO-FUNCTIONAL PHENOTYPE		ORGAN/SYSTEM INVOLVEMENT		GENETIC INHERITANCE PATTERN		ETIOLOGY		STAGE	
	D	Dilated	H	Heart <i>LV=left ventricle</i> <i>RV=right ventricle</i> <i>RLV=biventricular</i>	N	Family history negative	G	Genetic cause	ACC-AHA	stage represented as letter A, B, C, D
	H	Hypertrophic			U	Family history unknown	OC	Obligate carrier		
	R	Restrictive			AD	Autosomal dominant	ONC	Obligate non-carrier		
	R EMF	Endomyocardial fibrosis <i>LV=left ventricle</i> <i>RV=right ventricle</i> <i>RLV=biventricular</i>	M	Muscle (skeletal)	AR	Autosomal recessive	DN	<i>De novo</i>		
			N	Nervous	XLD	X-linked dominant	Neg	Genetic test negative for the known familial mutation	NA	not applicable
			C	Cutaneous	XLR	X-linked recessive	N	Genetic defect not identified	NU	not used
			E	Eye, Ocular	XL	X-linked	O	No genetic test, any reason*		
	A	ARVC <i>M=major</i> <i>m=minor</i> <i>c=category</i> <i>LV= left ventricle</i> <i>RV=right ventricle</i> <i>RLV=biventricular</i>	A	Auditory	M	Matrilineal	G-A-TTR	Genetic amyloidosis	followed by NYHA class represented as Roman numeral I, II, III, IV	
			K	Kidney	O	Family history not investigated*	G-HFE	Hemochromatosis		
			G	Gastrointestinal	Undet	Inheritance still undetermined	Non-genetic etiologies:			
			Li	Liver	S	Phenotypically Sporadic (apparent or real)	M	Myocarditis		
			Lu	Lung			V	Viral infection (add the virus identified in affected heart)		
	NC	LVNC	S	Skeletal			AI	Autoimmune/immune-mediate; suspected (AI-S), proven (AI-P)		
	E	Early, with type in parentheses	O	Absence of organ/system involvement*, e.g. in family members who are healthy mutation carriers; the mutation is specified in E and inheritance in G			A	Amyloidosis (add type: A-K, A-L, A-SAA)		
	NS	Nonspecific phenotype					I	Infectious, non viral (add the infectious agent)		
	NA	Information non available					T	Toxicity (add cause/drug)		
	O	Unaffected*					Eo	Hypereosinophilic heart disease		
							O	Other		

FIGURE 57-3 MOGES system for classification of cardiomyopathies. (Reproduced with permission from Arbustini E, Narula N, Tavazzi L, et al. The MOGE(S) classification of cardiomyopathy for clinicians, *J Am Coll Cardiol.* 2014 Jul 22;64(3):304-318.)

- 57-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 57*). This patient is a carrier for a mutation in LMNA. Although she has not developed a morphofunctional phenotype, patients with cardiac laminopathies are at risk for arrhythmias, both ventricular and supraventricular (option A). The other options reflect risks associated with cardiomyopathy in general.
- 57-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 57*) This patient has a dilated cardiomyopathy (M_D) with NYHA class IV symptoms (S_{D-IV}) (options A and B). The patient is believed to have a genetic etiology with an autosomal dominant pattern of inheritance (G_{AD}). However, the genetic defect is not known (E_{G-N-}) (options C and D).

- 57-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 57*) The color code describes possible and probable pathologic genetic mutations in red; genetic variants of unknown significance in yellow; and single-nucleotide polymorphisms with possible functional significance in green (option B). The others options are a part of the MOGES system but do not use color.
- 57-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 57*) This patient has a dilated cardiomyopathy (M_D) secondary to sarcoidosis ($E_{AI-Sarcoid}$) (options A and B). His sarcoid also involves his lungs (O_{Lu}) (option C). He has stage B heart failure and NYHA class I symptoms and therefore has asymptomatic left ventricular dysfunction (option A).

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CHAPTER 58

Dilated Cardiomyopathy

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 58-1.** A 42-year-old man presents to your clinic to establish care for a newly diagnosed dilated cardiomyopathy (DCM). His previous evaluation is notable for the absence of coronary artery disease. Review of his family history reveals that his father also had DCM and his sister has DCM. Which of the following is *not true* about familial DCM?
- A. DCM is familial in more than 60% of cases
 - B. This patient has an X-linked cardiomyopathy allele
 - C. The most common cause of familial DCM is mutations to sarcomeric genes
 - D. Of the nuclear envelope genes, mutations to LMNA most often result in DCM
 - E. Most DCM genes also cause other types of cardiomyopathy
- 58-2.** A 43-year-old woman is found to have a mutation of *LMNA2* associated with DCM. An echocardiogram reveals an ejection fraction of 40%. Which of the following is *true* of cardiac laminopathies that occur due to mutations of *LMNA2*?
- A. Conduction system disease often presents prior to DCM
 - B. Progression of the PR interval is associated with cardiac laminopathies due to mutations of *LMNA2*
 - C. Patients with cardiac laminopathies due to mutations of *LMNA2* are at high risk for ventricular tachycardia and sudden death
 - D. Prophylactic ICD implantation would be indicated for this patient if she demonstrated nonsustained ventricular tachycardia on ambulatory ECG monitoring
 - E. All of the above
- 58-3.** A 24-year-old woman with systemic scleroderma develops exertional dyspnea associated with pedal edema, paroxysmal nocturnal dyspnea, and orthopnea. Which of the following is *not* an associated cardiac manifestation of scleroderma?
- A. Hypertrophic cardiomyopathy
 - B. Pericardial effusion
 - C. Left ventricular (LV) systolic and diastolic dysfunction
 - D. Pulmonary hypertension
 - E. Interstitial fibrosis
- 58-4.** A 37-year-old woman presents with new-onset shortness of breath and orthopnea. She is noted to have an ejection fraction of 30%. Her history is remarkable for having recently delivered a baby boy 4 months ago. Which of the following is needed for a diagnosis of peripartum cardiomyopathy?
- A. The cardiomyopathy must be an idiopathic condition
 - B. The onset of the cardiomyopathy must be related to the timing of pregnancy
 - C. There should be no preexisting heart disease
 - D. There must be LV dysfunction
 - E. All of the above
- 58-5.** A 54-year-old man is admitted for a newly diagnosed cardiomyopathy. His past medical history is notable for heavy alcohol use. Which of the following is *true* of an alcohol-induced cardiomyopathy?
- A. Administration of thiamine can reverse the cardiomyopathy
 - B. A daily alcohol intake of > 80 grams per day (3 drinks) for five years prior to diagnosis is associated with cardiomyopathy
 - C. A hypertrabeculated phenotype
 - D. Occurrence of atrial fibrillation is associated with poorer outcomes

E. None of the above

58-6. You are asked to provide a preoperative risk assessment for a 38-year-old man with cirrhosis who is scheduled for transjugular intrahepatic portosystemic shunt (TIPS). Which of the following is *true* of cirrhotic cardiomyopathy?

- A. During the early phase of cardiomyopathy, diastolic dysfunction is apparent
- B. QT prolongation is present in more than 50% of cases
- C. Diastolic dysfunction predicts death after TIPS implantation
- D. Latent heart failure is often unmasked by stressors
- E. All of the above

58-7. You are asked to consult on the oncology ward for a possible chemotherapy-related cardiomyopathy. Which of the following is *not true* about chemotherapy-related cardiomyopathies?

- A. Anthracyclines are associated with type 1 myocardial damage
- B. Trastuzumab is associated with type 2 myocardial damage
- C. Cyclophosphamide is associated with a hemorrhagic myocarditis
- D. Sumatinib is associated with hypertension
- E. The incidence of cardiomyopathy increases when trastuzumab is used without an anthracycline

58-8. Which of the following is associated with a reversible cardiomyopathy?

- A. Alcohol-induced cardiomyopathy
- B. Tachycardia-induced cardiomyopathy
- C. Takotsubo cardiomyopathy
- D. Viral myocarditis
- E. All of the above

58-9. A 37-year-old man is admitted for a new-onset cardiomyopathy. His EKG shows frequent premature ventricular contractions (PVCs). Which of the following is *not* associated with a PVC-induced cardiomyopathy?

- A. More than 10,000 PVCs per day are associated with LV dilation
- B. More than 20,000 PVCs per day are associated with reduced ejection fraction
- C. For patients with a PVC-induced cardiomyopathy, successful termination of the PVCs can reverse the cardiomyopathy
- D. Therapy for frequent PVCs in patients with idiopathic LV dysfunction modifies clinical outcomes
- E. PVC-induced cardiomyopathy can occur in children

58-10. Which of the following is *not* associated with a mitochondrial cardiomyopathy?

- A. Hypertrophic phenotype
- B. Dilated phenotype
- C. Maternal inheritance
- D. Autosomal inheritance
- E. Clinical manifestations tend to be restricted to the heart

ANSWERS

58-1. The answer is B. (*Hurst's The Heart, 14th Edition, Chap. 58*) In more than 60% of cases of DCM, the disease is familial, as proven by clinical family screening demonstrating that more than one member is affected or shows traits that predict the development of the disease (option A).^{1,2} This patient likely has an autosomal dominant allele. This patient's father is affected, and because he did not inherit an X chromosome from his father, the disease allele cannot be X-linked (option B). Sarcomere genes (*TTN*, *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*, *MYL2*, *MYL3*) are mutated in 25% to 30% of DCM patients (option C).³ Nuclear envelope genes (*LMNA*, *EMD*, *SYNE1*, *TMPO*) are mutated in about 7% to 10% of cases, with *LMNA* mutations accounting for the majority of DCM in this subgroup (option D).⁴ Most DCM genes also cause other types of cardiomyopathy (HCM, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (option E).

58-2. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 58*) The development of conduction system disease usually precedes the appearance of the DCM (option A). The natural history is characterized by a long asymptomatic phase in which regular and slowly progressive LV dilation or dysfunction is demonstrated (option B).⁵ The high risk of life-threatening ventricular arrhythmias is one of the characteristics of cardiomyopathies, and such arrhythmias may manifest even in mildly dilated and dysfunctioning hearts.^{6,7} Recent guidelines on the primary prevention of sudden cardiac death (SCD) recommend ICD implantation in patients with DCM and a confirmed disease-causing *LMNA*

mutation and such clinical risk factors (Class IIa level B) as nonsustained ventricular tachycardia during ambulatory ECG monitoring, LV ejection fraction (LVEF) < 45% on initial evaluation, male gender, and nonmissense mutations (insertion, deletion, truncation, or mutations affecting splicing) (options C and D).

- 58-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 58*) The heterogeneous cardiac manifestations of scleroderma include myocarditis, pericarditis, and pericardial effusion (option B); conduction disturbances; LV systolic and diastolic dysfunction (option C); valve dysfunction; myocardial ischemia and coronary artery disease; and pulmonary hypertension (option D).⁸ Histologically, scleroderma is associated with fibrosis (option E). Hypertrophic cardiomyopathy is not typically associated with scleroderma (option A).
- 58-4. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 58*) Criteria for diagnosing peripartum cardiomyopathy include: (1) idiopathic condition (no detectable cause of HF) (option A); (2) temporal appearance (the last month of pregnancy or during the first 5 months postpartum according to NHLBI and toward the end of pregnancy or in the months following delivery according to ESC (option B); (3) the absence of preexisting known heart disease (option C); and (4) the presence of LV dysfunction (option D).
- 58-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 58*) The three criteria for diagnosing alcoholic cardiomyopathy include DCM phenotype, absence of other known and detectable causes of DCM (option C), and a long history of heavy alcohol intake. The toxic effect is expected for daily alcohol consumption over 80 g (three or more standard-sized drinks per day) lasting 5 years or more before the onset or diagnosis (option B).⁹ Atrial fibrillation, QRS width > 120 ms, and the absence of β -blocker therapy identify patients with a poor outcome (option D). Thiamine deficiency (beriberi) is no longer confused with alcoholic cardiomyopathy; the former fully responds to thiamine administration, whereas the latter does not (option A).
- 58-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 58*) According to the 2005 World Congress of Gastroenterology, cirrhotic cardiomyopathy is defined by "chronic cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease."¹⁰ The impaired diastolic relaxation is more common in early phases, whereas systolic dysfunction and LV dilation are manifest in advanced phases (option A); electrophysiological abnormalities include prolongation of QT interval in more than 50% of cases (option B), electromechanical dyssynchrony, and chronotropic and/or inotropic incompetence.¹¹ In the complex pathophysiology of cirrhosis-related cardiac and hemodynamic changes, diastolic dysfunction seems to predict death after TIPS implantation (option C).¹² Patients with cirrhosis often demonstrate hyperdynamic circulation and increased cardiac output, decreased systemic vascular resistance, and increased compliance of the arterial vessels. This combination of hemodynamic conditions corresponds to latent left HF where any stressor may clinically unmask the LV dysfunction (option D).
- 58-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 58*) Heart muscle toxicity is generally characterized as *nonreversible injury* (type 1) as a result of the presence of structural damage (prototyped by the anthracycline or high-dose cyclophosphamide DCM in acute and chronic forms) and potentially reversible (on cessation of therapy) dysfunction (type 2) in the absence of structural abnormalities, as with targeted therapies (ie, trastuzumab, sunitinib, lapatinib) (options A and B). The 3-year cumulative incidence of cardiomyopathy is 6.6% when trastuzumab is used with anthracyclines and 5.1% when used without anthracyclines (option E).¹³ Myocarditis is a rare complication described in patients treated for cancer (ie, cyclophosphamide and hemorrhagic myocarditis) (option C). Hypertension is the most common cardiovascular complication associated with vascular endothelial growth factor inhibitors (option D).
- 58-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 58*). All of the above are associated with a reversible cardiomyopathy (options A through D), although reversal of the cardiomyopathy is not guaranteed with cessation of the cause.
- 58-9. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 58*) A dose-response relationship has been demonstrated in serial evaluations of LV function among 239 consecutive patients with frequent PVCs and no obvious cardiac disease; > 20,000 PVCs per 24 hours were associated with subclinical deterioration in LVEF whereas >10,000 PVCs per 24 hours showed LV dilation without a change in LVEF (options A and B).¹⁴ For patients with a PVC-induced cardiomyopathy, successful termination of the PVCs can reverse the cardiomyopathy (option C). Randomized trials are ongoing, aimed at assessing whether therapy for frequent PVCs in patients with idiopathic LV dysfunction modifies clinical outcomes (option D). In children, the proportion of PVC-induced cardiomyopathy seems higher than previously expected, especially because ectopy tends to persist throughout follow-up (option E).
- 58-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 58*) Mitochondrial cardiomyopathies can be caused by mutations both in mitochondrial DNA genes (maternal inheritance) and in nuclear genes (Mendelian inheritance: no male passes down the disease to children) coding mitochondrial proteins (options C and D). They are characterized by either a hypertrophic phenotype evolving through dilated and dysfunctional hearts or DCM (options A and B). They are commonly observed in families in which mutation carriers also express noncardiac traits, such as hearing loss, palpebral ptosis, myopathy, renal failure, cryptogenic stroke, diabetes, optic neuritis, and/or retinitis pigmentosa (option E).

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CHAPTER 59

Hypertrophic Cardiomyopathies

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 59-1.** A 25-year-old woman seeks to establish care for hypertrophic cardiomyopathy (HCM). Her family history is notable for multiple affected family members. Which of the following is *not true* regarding the genetics of HCM?
- A. She is most likely to have a mutation of a sarcomeric protein
 - B. 5% to 10% of cases are caused by metabolic or storage disorders
 - C. Missense single nucleotide variants of *MYH7* are associated with a dominant negative effect
 - D. Nonsense mutations of *MYBC3* are associated with haploinsufficiency
 - E. Unaffected family members cannot have the causal mutation
- 59-2.** You are asked to be an expert witness at a trial for an 18-year-old man who experienced sudden death while playing basketball. Which of the following autopsy findings are *not* consistent with a diagnosis of HCM?
- A. Asymmetric septal hypertrophy with a small left ventricular cavity
 - B. If left ventricular outflow tract obstruction was present, plaque may be located on the upper septal area
 - C. Mitral valve abnormalities are rarely present
 - D. Epicardial arteries can follow an intramural course
 - E. Histopathologic examination shows cardiomyocyte hypertrophy and disarray
- 59-3.** A 24-year-old woman with HCM is on a maximally tolerated dose of beta-blocker and continues to have class III exertional dyspnea. Which of the following are causes of diastolic dysfunction in patients with HCM?
- A. Impairment of ventricular relaxation
 - B. Increased chamber stiffness
 - C. Insufficient coronary blood flow
 - D. Compromised myocardial energy metabolism
 - E. All of the above
- 59-4.** Which of the following physical examination findings are *not* associated with HCM with obstruction?
- A. Pulsus alternans
 - B. Bifid apical impulse
 - C. Decrease in murmur quality going from sitting to standing
 - D. Decrease in the murmur when raising the legs
 - E. Amyl nitrite will increase the murmur
- 59-5.** A 27-year-old man presents to your office for exertional syncope and shortness of breath. Which of the following would be consistent with a diagnosis of sarcomeric HCM?
- A. Left ventricular wall thickness > 10 mm
 - B. Diffuse subendocardial late gadolinium enhancement on cardiac MRI
 - C. Systolic anterior motion (SAM) of the mitral valve apparatus to cause obstruction
 - D. Short PR interval, pre-excitation, and extreme left ventricular hypertrophy (LVH) on ECG
 - E. Increased serum creatine phosphokinase (CPK) and lactate
- 59-6.** Your patient with HCM is in the cardiac catheterization laboratory for hemodynamic assessment and has the tracing shown in [Figure 59-1](#). Which of the following maneuvers can elicit this phenomenon?

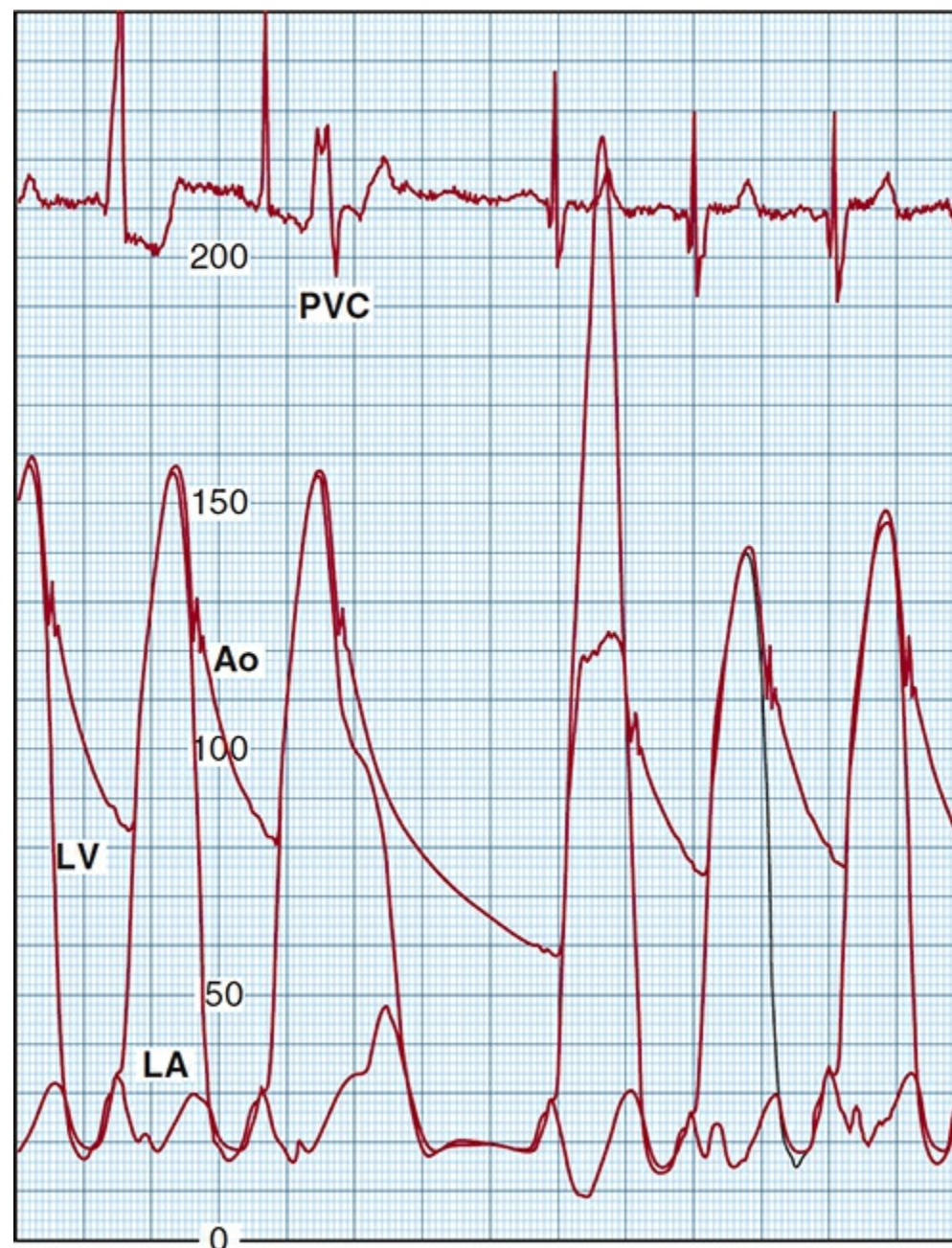


FIGURE 59-1 Invasive hemodynamic tracings for question 59-6.

- A. Valsalva
- B. Norepinephrine infusion
- C. Isooproterenol infusion
- D. A and C
- E. A and B

59-7. Your patient with HCM has several questions about his risk for sudden death (SCD). Which of the following features are *not* associated with an increased risk of SCD with HCM?

- A. History of prior cardiac arrest or spontaneous sustained ventricular tachycardia
- B. A family history of premature SCD in a first-degree relative with HCM
- C. Nonsustained ventricular tachycardia on ambulatory testing
- D. Hypertensive blood pressure response to exercise
- E. Extreme LVH > 30 mm

59-8. A 32-year-old man presents for exertional dyspnea. His echocardiogram is diagnostic of hypertrophic obstructive cardiomyopathy (HOCM). He is currently *not* taking any medications. Which of the following could be recommended?

- A. Fluid restriction
- B. Initiation of a beta-blocker
- C. Verapamil
- D. Alcohol septal ablation
- E. Surgical myectomy

59-9. A 44-year-old woman with HOCM continues to have class 3 shortness of breath despite maximal medical therapy. Which of the following are indications for myectomy?

- A. An LV outflow tract obstructive gradient ≥ 50 mm Hg
- B. New York Heart Association functional class III-IV symptoms despite maximal medical therapy
- C. Recurrent exertional syncope despite maximally tolerated drug therapy
- D. A and B
- E. All of the above

59-10. A 44-year-old woman with HOCM continues to have class III shortness of breath despite maximal medical therapy and

is interested in myectomy. Which of the following is *not true* regarding complications of myectomy?

- A. In large-volume centers, the operative mortality for septal myectomy is < 1%
- B. Complications of surgical myectomy (AV nodal block, ventricular septal defect, and aortic regurgitation) of surgery are uncommon
- C. The major complication of alcohol septal ablation is complete heart block
- D. The risk for complete heart block following alcohol septal ablation is increased if right bundle branch block is present prior to the ablation procedure
- E. A maximum LV wall thickness < 16 mm at the point of leaflet-septal contact is a risk factor for ventriculoseptal defects in both alcohol septal ablation and myectomy

ANSWERS

- 59-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 59*) The majority of mutations that cause HCM involve sarcomeric proteins. Between 75% and 80% involve cardiac myosin heavy chain (*MYH7*) and cardiac myosin binding protein C (*MYBPC3*). Mutations in cardiac troponin T (*TNNT2*), troponin I (*TNNI3*), α -tropomyosin (*TPM1*), myosin light chains (*MYL2*, *MYL3*), and cardiac actin (*ACTC1*) account for 15% to 20% of mutation-positive individuals (option A).¹ A further 5% to 10% of cases are caused by metabolic or storage disorders (eg, Anderson-Fabry disease, mitochondrial disorders, glycogen storage diseases), neuromuscular disorders, chromosome abnormalities, and genetic syndromes such as cardio-facial-cutaneous syndromes, including Noonan and LEOPARD syndromes (option B).² Two pathogenic mechanisms are thought to account for disease associated with mutations in cardiac sarcomere proteins. Missense single nucleotide variants (a nucleotide change that results in an amino acid being substituted by another amino acid in the protein) predominantly lead to a *dominant negative effect* (described as a “poison peptide” mechanism) in which the mutated protein is not destroyed but rather integrates into the sarcomere, leading to the disease phenotype; this is thought to be characteristic of *MYH7* variants (option C). Alternatively, nonsense single nucleotide variants or small frameshift insertion-deletions can introduce a premature stop codon and cause haploinsufficiency as a result of nonsense mRNA-mediated decay or proteolysis of a truncated (just partially translated) protein. This mechanism is believed to be typical of the majority of *MYBPC3* disease-causing mutations (option D).³ HCM is characterized by variable intra- and interfamilial expression and incomplete and age-dependent clinical penetrance. Thus, unaffected family members can be carriers of the causal mutation (option E).⁴
- 59-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 59*) Gross examination of the heart in patients with HCM demonstrates asymmetric septal hypertrophy with a small left ventricular cavity (option A).⁵ The mural endocardium may be thickened by fibrous tissue, and if left ventricular outflow tract obstruction is present, there is often a plaque located on the upper septal area where the mitral valve repeatedly has come in contact with the septum (option B). The mitral valve itself may be abnormal, with elongation of the mitral chordae and anterior displacement of hypertrophied papillary muscles. Abnormal attachments of the mitral valve chordae into the septum, insertion of the papillary muscle head directly into the mitral leaflets, myocardial clefts, and increased ventricular trabeculation are also common (option C).⁶ Although the epicardial coronary arteries are usually normal, they can follow an intramural course and be compressed during ventricular systole (option D).⁷ The classic histopathologic appearance of HCM consists of cardiomyocyte hypertrophy and disarray, interstitial and replacement fibrosis, and dysplastic arterioles (option E).⁸
- 59-3. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 59*) Diastolic dysfunction arises from multiple factors that affect both ventricular relaxation and chamber stiffness (options A and B).⁹ Patients with HCM have increased oxygen demand as a result of ventricular hypertrophy and abnormal loading conditions but also have compromised coronary blood flow to the LV myocardium because of abnormally small and partially obliterated intramural coronary arteries (option C). In addition, myocardial energy metabolism is compromised as a result of inefficient cardiomyocyte contraction and is an early feature of the disease in carriers of sarcomeric protein mutation (option D).¹⁰
- 59-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 59*) The classic carotid pulsation is brisk with a spike-and-dome pattern, characterized by a rapid rise (percussion wave) followed by a midsystolic drop that is, in turn, followed by a secondary wave (tidal wave). Pulsus alternans is alternating strong and weak beats, often associated with severe LV dysfunction (option A). The apical impulse is almost always abnormal in patients with HCM. Typically, it is a sustained systolic thrust that continues throughout most of systole and can be bifid as a result of a forceful atrial systole (option B). From the standing position to a prompt squat, the murmur will markedly decrease in intensity as a result of increases in afterload and preload (option C). Other maneuvers that are used to change the intensity of the murmur include leg-raising to increase preload (and thereby decrease the intensity of the murmur) and inhaling amyl nitrite to decrease afterload (options D and E).
- 59-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 59*) Increased LV wall thickness measured by any imaging technique is the basis for the diagnosis of HCM. In adults, a wall thickness ≥ 15 mm at end-diastole in one or more

myocardial segments and, in children, a wall thickness more than two standard deviations greater than the predicted mean are sufficient to make the diagnosis (option A). Diffuse subendocardial late gadolinium enhancement on cardiac MRI is suggestive of amyloid. HCM typically has midwall late gadolinium enhancement or late gadolinium enhancement at the insertion zones of the right ventricle (RV) in the septum (option B). Dynamic LV outflow tract obstruction (LVOTO) is characterized by SAM of the mitral valve apparatus and an open ventricular chamber. Most patients have SAM of the anterior leaflet, but it also occurs with the posterior leaflet.¹¹ Short PR interval, pre-excitation, and extreme LVH on ECG are more consistent with Danon's disease or glycogen storage disease (option D). Increased serum CPK and lactate tend to go along with mitochondrial myopathies (option E).

- 59-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 59*) Figure 59-1 shows the Brockenbrough phenomenon—the hallmark of latent obstruction. After a premature contraction, an increase in the contractility of the ventricle results in a marked increase in the degree of dynamic obstruction. This is seen as an increase in the outflow gradient and a decrease in the aortic pulse pressure after the pause. When there is little resting obstruction, provocation using the Valsalva maneuver or infusion of isoproterenol can be performed in the catheterization laboratory (options A and C). Norepinephrine infusion would increase afterload and is unlikely to increase obstruction (option B).
- 59-7. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 59*) Several clinical features are associated with a high risk for SCD in patients with HCM.¹² Patients who have had a prior cardiac arrest or spontaneous sustained ventricular tachycardia are at highest risk (option A). A family history of premature SCD in a first-degree relative with HCM portends a high risk, particularly if there are multiple occurrences (option B). Other risk markers include recent unexplained syncope, nonsustained ventricular tachycardia (option C), hypotensive blood pressure response to exercise (option D), and extreme LV hypertrophy (> 30 mm) (option E).
- 59-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 59*). Patients with LVOTO should maintain hydration at all times, avoid excessive alcohol consumption, and maintain a healthy weight (option A).¹² Medical therapy should be considered the first-line therapy for the relief of symptoms in patients with obstructive HCM. Beta-adrenergic blocking agents are usually the drugs of choice. Theoretic actions of beta-blockers include decreased heart rate response to exercise, relief of angina by a decrease in myocardial oxygen demand, and improvement in diastolic filling time (option B). Nondihydropyridine calcium channel blockers—specifically, verapamil and diltiazem—are also of value in the treatment of HCM, particularly if beta-blockers are contraindicated or ineffective (option C). A trial of medical therapy should be offered before considering alcohol septal ablation or surgical myectomy (options D and E).
- 59-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 59*) For patients who have an LV outflow tract obstructive gradient ≥ 50 mm Hg (option A), moderate-to-severe symptoms (New York Heart Association functional class III-IV) (option B), or recurrent exertional syncope despite maximally tolerated drug therapy (option C), other treatment options such as septal myectomy, septal ablation, or dual-chamber pacing should be considered.¹²
- 59-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 59*) In large-volume centers, the operative mortality for septal myectomy is < 1% (option A).¹³ Complications of myectomy (AV nodal block, ventricular septal defect, and aortic regurgitation) of surgery are uncommon (option B).¹² The major complication of alcohol septal ablation is complete heart block, which, with small doses of alcohol and guidance with myocardial contrast echocardiography, occurs in 7% to 20% of patients (option C). The risk for heart block is increased in patients with a preexisting LBBB (option D). A maximum LV wall thickness < 16 mm at the point of leaflet-septal contact is a risk factor for ventriculoseptal defects in both alcohol septal ablation and myectomy.¹²

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CHAPTER 60

Left Ventricular Noncompaction

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 60-1.** Which of the following imaging findings is consistent with a diagnosis of left ventricular noncompaction (LVNC)?
- A. A ratio of noncompacted myocardium to compact myocardium > 2 in the parasternal short axis by echocardiography
 - B. A ratio of noncompacted myocardium to compact myocardium > 2.3 in the horizontal long axis by cardiac MRI
 - C. A ratio of noncompacted myocardium to compact myocardium > 1 in at least two segments of short axis images by multidetector CT
 - D. All of the above
 - E. A and B
- 60-2.** A 57-year-old man presents to your clinic to follow up a negative cardiac MRI (CMR) stress test for nonspecific chest pain. He was noted to have an increased ratio of noncompact to compact myocardium with normal left ventricular (LV) function. He is otherwise healthy. Which of the following is *not true* about compact and trabecular myocardium in the normal population?
- A. The compacted layer but not the trabeculated layer is thicker in men than in women
 - B. The compacted layer thickens, whereas the trabeculated layer thins with systole
 - C. Trabeculated LV segments show increased systolic thinning of trabeculated layers and greater thickening of the compact segments with age
 - D. There are sex-specific differences in the trabeculated/compacted ratio at end systole or end diastole
 - E. In end systole, the trabeculated/compacted ratio is lower in older (50–79 years) subjects than in younger (20–49 years) subjects
- 60-3.** Which of the following is *not true* regarding the proposed pathogenesis of LVNC?
- A. LVNC may be the result of abnormal cardiac development
 - B. Polymorphisms of genes affecting the Notch pathway are associated with LVNC
 - C. The causes of interruption of myocardial compaction during cardiac development are unknown
 - D. LVNC is always inherited and never acquired
 - E. LVNC can be regarded as an isolated entity or as one of the traits that may recur in other cardiac and noncardiac diseases
- 60-4.** A 32-year-old woman with a history of Barth syndrome in her family is pregnant with a boy. She wants to know about the risks of Barth syndrome if her son is affected. Which of the following is *true* of Barth syndrome?
- A. Barth syndrome is not transmitted from mother to son
 - B. Barth syndrome is due to a mutation of the *MIB1* gene
 - C. Hypertrophic cardiomyopathy does not occur with Barth syndrome
 - D. Among children with a dilated cardiomyopathy (DCM), reverse remodeling can occur with normalization of heart function
 - E. Arrhythmias are uncommon
- 60-5.** Which of the following is *not true* about the genetic basis for LVNC?
- A. LVNC can result from mutations to genes that encode sarcomeric proteins
 - B. The same mutations that cause LVNC can result in hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and restrictive cardiomyopathy (RCM)
 - C. LVNC can be seen in patients with neuromuscular disorders
 - D. LVNC has been associated with mutations of ion channels
 - E. All of the above are true

- 60-6.** A 34-year-old athlete is referred to you for palpitations. CMR showed a LVNC phenotype with normal left ventricular function. Which of the following is *true* of acquired LVNC?
- A. LVNC is a rare finding among athletes
 - B. The majority of women who develop LVNC during pregnancy will have a regression of trabeculation after delivery
 - C. Patients with siderosis and LVNC have preferential accumulation of iron in the compact layer
 - D. LVNC is rare among patients with bicuspid aortic valve disease
 - E. Patients with acquired LVNC are likely to have an underlying familial syndrome
- 60-7.** Which of the following is a typical finding in the evaluation of LVNC?
- A. An abnormal ECG
 - B. A ratio of > 2:1 of noncompacted to compacted layer at end diastole by echo
 - C. Myocardial fibrosis is identified by late gadolinium enhancement during CMR
 - D. Elevation of troponin in the serum
 - E. All of the above are typical findings
- 60-8.** A 45-year-old man presents for evaluation of LVNC. He is asymptomatic but was found to incidentally have an ejection fraction of 35% and LVNC. Which of the following is *true* about the prognosis for patients with LVNC?
- A. Asymptomatic patients or individuals with LVNC and normal LV function have a poor prognosis
 - B. Patients presenting with heart failure (New York Heart Association class III or IV), sustained ventricular arrhythmias, or left atrial dilation have a favorable prognosis
 - C. A right bundle branch block is associated with a good prognosis
 - D. Prognosis depends on the severity of the underlying cardiac disease rather than the trabecular anatomy of the LV
 - E. None of the above are true
- 60-9.** Which of the following is *not* indicated in patients with Barth syndrome?
- A. Consideration of aspirin with severe LV dysfunction
 - B. Inclusion of uncooked cornstarch in the diet to prevent muscle protein loss
 - C. Avoidance of succinylcholine
 - D. Use of prophylactic antibiotics in high-risk clinical situations
 - E. Empiric administration of warfarin with a goal INR of 2-3
- 60-10.** Which of the following is *true* regarding the epidemiology of LVNC?
- A. The incidence of LVNC in children is less than 0.1 per 100,000.
 - B. Approximately 10% of pediatric cardiomyopathies are associated with LVNC
 - C. LVNC is more common in women than in men
 - D. A and B
 - E. A and C

ANSWERS

- 60-1. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 60*) A ratio of noncompacted myocardium to compact myocardium > 2 by echocardiography is consistent with a diagnosis of LVNC (option A).¹ A ratio of noncompacted myocardium to compact myocardium > 2.3 in the horizontal long axis by cardiac MRI is consistent with a diagnosis of LVNC (option B).² A ratio of noncompacted myocardium to compact myocardium > 2.2 in at least 2 segments of short axis images by cardiac CT is consistent with a diagnosis of LVNC (option C).²
- 60-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 60*) CMR studies in normal adult volunteers demonstrated the following sex- and age-related differences: (1) the compacted but not the trabeculated layer is thicker in men than in women (option A); (2) the compacted layer thickens, whereas the trabeculated layer thins with systole (option B); (3) trabeculated LV segments show increased systolic thinning of trabeculated layers and greater thickening of the compact segments ($P < .05$) with age (option C); (4) total wall thickening is neither sex nor age dependent; (5) there were no sex-specific differences in the trabeculated/compacted ratio at end systole or end diastole (option D); and (6) in end systole, the trabeculated/compacted ratio was lower in older (50–79 years) subjects than in younger (20–49 years) subjects ($P < .05$) (option E).³ Overall, the application of current diagnostic criteria demonstrates that LVNC may occur in a relevant proportion of healthy individuals.
- 60-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 60*) The most cited pathogenetic hypothesis for LVNC is embryogenic arrest of the normal process of trabecular maturation during early intrauterine life when the heart undergoes

cardiac chamber maturation (option A).⁴ However, LVNC can be heritable or acquired. For example, patients with cardiomyopathies may develop LVNC during the course of their disease (option D).^{5,6} While many signaling pathways have been linked to compaction during heart development, only mutations of the *MIB1* gene have been linked to LVNC. The *MIB1* gene encodes a ubiquitin ligase that regulates endocytosis of Notch ligands.⁷ To date, mutations in this gene have been reported in individuals with LVNC in two Spanish families (option B).⁸ The causes of interruption of myocardial compaction are unknown (option D). LVNC can be regarded as an isolated entity or as one of the traits that may recur in other cardiac and noncardiac diseases. For example, LVNC is associated with tafazzinopathies [caused by mutations in the *TAZ* (*Tafazzin*, or *G4.5*) gene] (option E).⁹

- 60-4. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 60*) Barth syndrome should be suspected in all male infants with heart failure, DCM, and LVNC, especially when associated with other markers of disease. Barth syndrome is a rare X-linked recessive disorder characterized by cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and distinctive facial characteristics. As an X-linked disorder, the mutation is passed from mother to son (option A). While mutations of *MIB1* have been associated with LVNC, Barth syndrome is caused by mutations in the *G4.5* gene (*TAZ*) (option B).⁹⁻¹¹ LVNC is commonly associated with LV dilation and dysfunction at onset.⁹ Less commonly, Barth cardiomyopathy may present with a hypertrophic or hypertrophic-dilated phenotype (option C). Heart involvement occurs in almost all children before the age of 5 years. Thereafter, the cardiomyopathy may demonstrate an intermittent course during which the heart can undergo remodeling. Improvement can be observed after infancy, with possible stabilization after the toddler years (option D).¹² Overall, however, cardiac function varies and tends to decline over time. Arrhythmias, both supraventricular and ventricular, are more commonly reported in adolescents and young adults than in infants.⁹
- 60-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 60*) LVNC can result from a diverse set of mutations, including to sarcomeric proteins (option A), ion channels (option D), and neuromuscular disease loci (option C). Mutations to the sarcomeric proteins ACTC1 (cardiac actin alpha) and MYH7 can cause DCM, RCM, and HCM (option B).^{13,14}
- 60-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 60*) The proportion of athletes who develop LVNC under intensive exercise is relevant (about 10%) (option A).¹⁵ Among pregnant women with LVNC, 69.2% showed complete resolution of LV trabeculations over a mean duration of 8.1 ± 4.2 months (option B).¹⁶ Although LVNC can be associated with disorders of red blood cells, in patients with myocardial iron overload and siderosis, a preferential distribution of intramyocyte iron in the compacted or noncompacted layers has not been observed (option C).¹⁷ A high prevalence of LVNC is reported in patients fulfilling the echocardiographic criteria for bicuspid aortic valve (BAV). Specifically, in one study, 12 (11.0%) of 109 patients with BAV fulfilled the criteria for LVNC, with nine of the 12 patients being men. Although the pathophysiologic basis of LVNC in patients with BAV is unclear, special attention should be given to the evaluation of LV trabecular anatomy.¹⁸ All these acquired conditions of LVNC demonstrate that a unique pathogenetic hypothesis of embryogenic defect is unlikely to explain acquired, late-onset, transient LVNC (option E).
- 60-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 60*) Although a normal ECG finding is rare in LVNC and is observed in a minority of patients (from 6% to 13%), there are no changes specific to LVNC (option A).¹⁹ A ratio of > 2:1 of noncompacted to compacted layer at end systole by echo is characteristic of LVNC (option B). Myocardial fibrosis is not a criterion for the diagnosis of LVNC (option C). There are no specific biomarkers for LVNC (option D).
- 60-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 60*) Prognosis in LVNC depends on the clinical presentation. Asymptomatic patients or individuals with LVNC and normal LV function have a good prognosis (option A).²⁰ Alternatively, patients presenting with heart failure (New York Heart Association class III or IV), sustained ventricular arrhythmias, or left atrial dilation have an unfavorable prognosis (option B).^{20,21} Adverse outcomes of isolated LVNC occur in patients with advanced heart failure, dilated left heart with systolic dysfunction, reduced systolic blood pressure, pulmonary hypertension, and right bundle branch block (option C).²⁰ In summary, prognosis depends on the severity of the underlying cardiac disease rather than the trabecular anatomy of the LV (option D).
- 60-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 60*) Patients diagnosed with Barth syndrome with heart failure should receive standard medications as per guidelines. Aspirin can eventually be added to decrease the risk of stroke in patients with severe LV dysfunction (option A). Empiric warfarin in the absence of thromboembolic events is not recommended (option E). The monitoring of arrhythmias and related prevention strategies should be maintained over the course of the patient's life. Disease-specific treatments can include the administration of granulocyte colony-stimulating factor either routinely or in high-risk clinical situations (eg, infections, surgery) along with prophylactic antibiotics (option D). Diets should include the administration of uncooked cornstarch to prevent muscle protein loss overnight (option B). Succinylcholine, a nondepolarizing neuromuscular blocker that could have a prolonged effect, should be avoided (option C).¹²
- 60-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 60*) The precise proportion of LVNC remains elusive. Data on the annual incidence of LVNC in children report values < 0.1 per 100,000 (option A).²² Isolated LVNC accounted for

9.2% of all cases in a population-based retrospective cohort study of primary cardiomyopathies in Australian children.²³ This prevalence was close to that recorded in the Texas Children's Hospital echocardiography database (9.5%) (option B).²⁴ As for sex, LVNC is reported to be more common in men (56% to 82%) than in women (option C).²⁵⁻²⁸

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CHAPTER 61

Restrictive Heart Diseases

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 61-1.** Which of the following echocardiographic findings are associated with restrictive physiology?
- A. An increased ratio of early diastolic filling to atrial filling (≥ 2)
 - B. Decreased E-deceleration time (< 160 ms)
 - C. Increased isovolumetric relaxation time
 - D. A and B
 - E. B and C
- 61-2.** Which of the following features are consistent with the European Society of Cardiology and American Heart Association definitions of restrictive cardiomyopathy?
- A. Normal or reduced diastolic volumes of one or both ventricles
 - B. Increased ventricular wall thickness
 - C. Normal or reduced systolic volumes of one or both ventricles
 - D. A and B
 - E. A and C
- 61-3.** A 43-year-old woman is admitted to your care for acute decompensated heart failure with preserved ejection fraction. The family history is notable for restrictive cardiomyopathy. She has experienced a nearly 25-pound weight gain, is orthopneic, and is short of breath at rest. Which of the following would you *not* expect to observe during her physical examination?
- A. Prominent jugular venous pulse and X and Y descents
 - B. Ascites
 - C. Crescendo-decrescendo murmur that worsens with Valsalva
 - D. A filling sound
 - E. Diminished pulse pressure
- 61-4.** Which of the following findings favor a diagnosis of constrictive pericarditis over restrictive cardiomyopathy?
- A. Elevated NT-proBNP
 - B. Kussmaul's sign
 - C. Shift of the septum with respiration by echocardiogram
 - D. Higher lateral e' velocity compared to the medial e'
 - E. Prominent y descent on the jugular venous waveform
- 61-5.** Which of the following is *true* regarding the genetic basis of RCM?
- A. Most cases are autosomal recessive
 - B. Mutations of *TNNI3* are associated with RCM
 - C. EMB demonstrating immunoreactive granulofilamentous material accumulated within myocytes is indicative of a typical RCM desminopathy
 - D. B and C
 - E. None of the above are true
- 61-6.** A 32-year-old woman presents to your clinic for volume overload. Her examination is notable for an elevated jugular venous pressure with prominent y descent. Her neck is also notable for the finding in [Figure 61-1](#). She also has ascites marked peripheral edema. Echocardiography shows a RCM. Family history is notable for family members with the same condition. Which of the following genes are associated with this condition?



FIGURE 61-1 Neck of the patient in question 61-6.

- A. *MYH6*
- B. *MYBC3*
- C. *ABCC6*
- D. *TNNI3*
- E. *TNNT2*

61-7. Which of the following is *not* characteristic of cardiac involvement of hereditary hemochromatosis (HH)?

- A. Serum ferritin > 300 ng/mL
- B. Low voltage on ECG
- C. Longer T2* times with cardiac MRI are associated with a better prognosis
- D. Diastolic dysfunction occurs early and is followed by reduced systolic function later in the disease
- E. Lower early (E') diastolic velocity by echocardiography

61-8. A 65-year-old man presents to your office for evaluation of cardiac amyloidosis. He had been having shortness of breath, and a cardiac MRI was suggestive of amyloid deposition. Which of the following would *not* be indicated to resolve the cause of his amyloid?

- A. Endomyocardial biopsy (EMB) with mass spectrometry of the sample
- B. Serum protein electrophoresis
- C. Serum free light chains
- D. No further testing, and referral for palliation
- E. Pro-BNP levels

61-9. A 54-year-old woman presents with cutaneous flushing, diarrhea, bronchospasm with wheezing and shortness of breath, and volume overload. You suspect carcinoid heart disease. Which of the following is indicated to make a diagnosis?

- A. Coronary angiography
- B. Serum serotonin, platelet serotonin, and urinary 5-hydroxyindoleacetic acid levels
- C. Serum ACE level
- D. Cardiopulmonary exercise testing
- E. Fecal evaluation for ova and parasites

61-10. A 73-year-old woman is diagnosed with AL amyloid complicated by cardiac involvement. She is referred to you for cardiac clearance prior to treatment consideration. Which of the following has prognostic value for this patient?

- A. Serum NT-proBNP
- B. Cardiac troponin T
- C. Evaluation of NYHA functional class
- D. A and B
- E. All of the above

ANSWERS

61-1. The answer is **D**. (*Hurst's The Heart, 14th Edition, Chap. 61*) Restrictive physiology describes a pattern of ventricular filling in which increased myocardial stiffness causes a precipitous elevation of ventricular pressure matched by a limited increase in volume; the resultant diastolic dysfunction is characterized by a pattern of mitral inflow Doppler velocities

with an increased ratio of early diastolic filling to atrial filling (≥ 2) (option A), decreased E-deceleration time (< 160 ms) (option B), and decreased isovolumetric relaxation time (option C).

- 61-2. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 61*) According to the definition of the European Society of Cardiology (ESC), "Restrictive cardiomyopathies are defined as restrictive ventricular physiology in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, and normal ventricular wall thickness."¹ According to the definition of the American Heart Association (AHA), "Primary restrictive non-hypertrophied cardiomyopathy is a rare form of heart muscle disease and a cause of heart failure that is characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular (LV) wall thickness and atrioventricular (AV) valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function."² Both definitions emphasize restrictive ventricular physiology, normal or reduced volume of one or both ventricles, and normal wall thickness.
- 61-3. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 61*) A physical examination of patients with RCM reflects the elevated systemic and pulmonary venous pressures, with prominent jugular venous pulse and X and Y descents. In the advanced course of the disease, the pulse volume is low, the stroke volume declines, and the heart rate increases. A systolic murmur and filling sound reflect AV valve regurgitation and fast early diastolic filling; a fourth heart sound (S4) can be present. Hepatomegaly, ascites, and peripheral edema are common in decompensated patients. A crescendo-decrescendo murmur that worsens with Valsalva is more consistent with a diagnosis of hypertrophic obstructive cardiomyopathy.
- 61-4. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 61*) It is crucial to distinguish between RCM and constrictive pericarditis (CP) because RCM typically responds only to medical management and carries a poor prognosis, whereas CP may be curable by pericardiectomy and represents a potentially reversible cause of heart failure.³ Two-dimensional echocardiography, M-mode, and Doppler blood-flow evaluation including respiratory-related ventricular septal shift (option C), preserved or increased medial mitral annular e' velocity (option D), and prominent hepatic vein expiratory diastolic flow reversal are independently associated with the diagnosis of CP.⁴⁻⁶ NT-proBNP levels are significantly higher in RCM than in CP (option A).⁷ Kussmaul's sign can be observed in CP or RCM (option B). CP is associated with a prominent x descent and y descent, while RCM is associated a prominent y descent but a blunted x descent (option E).
- 61-5. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 61*) Familial RCM demonstrates autosomal dominant inheritance in the majority of cases (option A). The *TNNI3* gene that encodes the thin filament troponin I is the most common disease gene responsible for RCM (option B).⁸ The typical RCM desminopathy is easily diagnosed by EMB demonstrating desmin immunoreactive granulofilamentous material accumulated within myocytes (option C).⁹
- 61-6. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 61*) This patient has pseudoxanthoma elasticum (PXE). PXE is a rare autosomal recessive systemic disease of the connective tissue that affects the extracellular matrix of multiple organs. PXE involves the cutaneous, ocular, and cardiovascular systems.^{10,11} The cutaneous lesions typically occur in flexural areas ([Figure 61-1](#)), and the fundi may show angioid streaks radiating out from the optic discs, subretinal neovascularization, and/or hemorrhage. The cardiovascular manifestations are characterized by the development of arterial calcifications, premature coronary artery disease, peripheral vascular disease, and RCM.¹²⁻¹⁷ PXE is caused by homozygous or compound heterozygous mutations in the *ABCC6* (ATP-binding cassette subfamily C member 6) gene that encodes a transmembrane adenosine triphosphate (ATP)-driven organic anion transporter (option C). Options A, B, D, and E are sarcomeric genes for which mutations are associated with hypertrophic cardiomyopathy and dilated cardiomyopathy.
- 61-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 61*) The cardiac phenotype of HH is characterized by early LV diastolic dysfunction with evolution through LV systolic dysfunction and dilation (option D). The diagnosis of HH is established by genetic testing in patients with elevated serum ferritin (> 300 ng/mL) and transferrin saturation values ($> 55\%$) (option A). The ECG is nonspecific and does not significantly contribute to the diagnosis of HH cardiomyopathy; low QRS complex voltage and nonspecific repolarization abnormalities are uncommon in early phases; conduction disease may be present (option B). With cardiac MRI, the T2* method is highly sensitive and specific and is especially useful for detecting, grading, and monitoring iron deposition.¹⁸⁻²⁰ Patients demonstrating a T2* higher than 20 ms are at low risk for developing heart failure (HF); T2* between 10 and 20 ms indicates the presence of cardiac iron deposition and an intermediate risk of HF; and a T2* less than 10 ms indicates high risk of HF and a need for immediate chelation therapy.²¹ Other modalities can suggest HH as well. In a multivariable analysis, echocardiographic spectral tissue Doppler lower early (E') diastolic velocity was independently associated with hemochromatosis.²²
- 61-8. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 61*) The gigantic scientific achievements in advancing our understanding of the biomolecular bases of amyloidogenic processes, and the development of novel drugs that target the different types of amyloidosis, are rapidly helping to change the fate of those with an ominous disease that until recently was hopeless and that is now a prototype of a successful model of precision and personalized medicine (option D). In the patient with unexplained LV hypertrophy and clinical suspicion for amyloidosis, biochemical testing should include evaluation for monoclonal protein production, serum immunofixation and electrophoresis, and serum free light chain

assay (options B and C).²³⁻²⁶ EMB has the dual advantage of being able to demonstrate amyloid deposition and to allow for the immune characterization of amyloidogenic protein. Recently, mass spectrometry–based proteomics have been introduced as a valuable tool for amyloid typing, with the advantage of not being antibody dependent. This can be performed on whole tissues or after laser capture microdissection of Congo red–positive areas (option A).²⁷ A high concentration of NT-proBNP allows the detection of AL amyloidosis at presymptomatic stages with a diagnostic sensitivity of 100%. Thus, screening with NT-proBNP has been advocated in patients at risk of developing AL amyloidosis (ie, patients followed by hematologists for monoclonal gammopathy of undetermined significance and altered circulating free light chain ratio).²⁸ Further, serum NT-proBNP levels are prognostic (option E).

- 61-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 61*) Carcinoid heart disease (Hedinger syndrome) is a rare condition that affects the right side of the heart in up to 60% of patients with neuroendocrine tumors (NETs) and systemic carcinoid syndrome (CS).²⁹ CS is caused by vasoactive substances secreted by NET cells; 5-hydroxytryptamine (serotonin) is the predominant peptide, followed by prostaglandins, histamine, bradykinin, tachykinins, and transforming growth factor- β (TGF- β). Both the tachykinins and TGF- β display profibrogenic properties inducing fibromyxoid plaques that affect the right ventricular endocardium, the ventricular side of the tricuspid valve apparatus (leaflets, chordae, and papillary muscles), the ventricular site of the pulmonary valve, and less commonly, the pulmonary artery. Serum serotonin, platelet serotonin, and urinary 5-hydroxyindoleacetic acid levels are elevated (option B).³⁰ The other options provided are helpful to exclude other causes of heart failure such as coronary artery disease (option A), shortness of breath (option D), sarcoid (option C), and diarrhea (option E). However, none of these are specific to the diagnosis of carcinoid.
- 61-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 61*) With AL amyloid, the criteria for evaluating both hematologic response (decreased amyloidogenic light chains) and organ response (improvement of organ function) are well established and graded. Treatment options depend on eligibility for autologous stem cell transplantation as well as on individual criteria to evaluate the tolerability of chemotherapeutic agents, including novel agent-based treatments with proteasome inhibitors, such as bortezomib, or immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide.³¹ Elevated cardiac biomarkers (NT-proBNP > 5000 ng/L, cardiac troponin T > 0.06 ng/mL) are considered exclusion criteria for stem cell transplantation (options A and B).³² Standard chemotherapy requires dose reductions in stage IIIb patients (option C). Non-chemotherapy approaches to the treatment of AL amyloidosis are now rapidly expanding.

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CHAPTER 62

Arrhythmogenic Cardiomyopathy

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 62-1.** A 35-year-old man experiences a sudden-onset syncope while playing soccer, and you are consulted by the emergency department. All of the following represent *major* criteria from the updated Task Force criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) *except*:
- A. Regional right ventricular akinesia on transthoracic echo
 - B. Inverted T waves in leads V1 and V2 in the absence of complete right bundle branch block
 - C. Nonsustained ventricular tachycardia with LBBB morphology and superior axis
 - D. Identification of a pathogenic mutation
 - E. Epsilon wave
- 62-2.** Which of the following regarding the prevalence of ARVC in the general population and the prevalence of clinical manifestations in men versus women respectively is *correct*?
- A. 1/1000 – 1/5000; males > females 5:1
 - B. 1/5000 – 1/10,000; males > females 5:1
 - C. 1/1000 – 1/5000; males > females 3:1
 - D. 1/1000 – 1/5000; females > males 3:1
 - E. 1/5000 – 1/10,000; females > males 5:1
- 62-3.** Classic right-sided ARVC is a genetic disease of the intercalated disks. Which of the following regarding intercalated disks is *incorrect*?
- A. Intercalated disks are the units of electromechanical continuity between cardiac myocytes
 - B. The sarcomere constitutes a component of the intercalated disk
 - C. Gap junctions constitute a component of the intercalated disk
 - D. Adherens junctions constitute a component of the intercalated disk
 - E. Desmosomes constitute a component of the intercalated disk
- 62-4.** A 30-year-old man presents to your clinic with bilateral lower extremity edema that has been progressive over the last few months. His physical exam reveals an elevated jugular venous pressure. In what percentage of ARVC cases do patients present with this physical finding?
- A. 5% to 10%
 - B. 20% to 30%
 - C. 30% to 40%
 - D. 50% to 60%
 - E. 70% to 80%
- 62-5.** A 25-year-old man presents to the hospital with rapid-onset palpitations. These lasted for approximately 10 minutes and were associated with dizziness. No documentation of a sustained arrhythmia was noted on monitoring, but he is noted to have frequent premature ventricular contractions of RBBB morphology, superior axis, and negativity in lead I. On physical exam, you note thickening of the skin on the palms of his hands. A transthoracic echocardiogram is performed and reveals left ventricular (LV) dilatation and dyskinesia. This constellation of findings is *most* consistent with:
- A. Anderson–Tawil syndrome
 - B. Naxos disease
 - C. Brugada syndrome
 - D. Catecholaminergic polymorphic ventricular tachycardia

E. Caravajal syndrome

- 62-6.** After you suspect ARVC in a 40-year-old woman, a cardiac MRI is performed. The conclusion in the final report notes, “an affected triangle of dysplasia, a pattern most consistent with ARVC. Correlate clinically.” The *triangle of dysplasia* refers to the combination of which of the following structures?
- A. Epicardial subtricuspid region, cavotricuspid isthmus, and right ventricular (RV) outflow tract
 - B. Left, right, and noncoronary cusps of the aortic valve
 - C. RV apex, interventricular septum, and LV apex
 - D. Epicardial subtricuspid region, RV basal anterior wall, and posterolateral left ventricle
 - E. Basal mitral valve region, RV basal anterior wall, and LV apex
- 62-7.** A 45-year-old woman has a diagnosis of nonischemic cardiomyopathy, with signs and symptoms of predominantly right-sided heart failure. You suspect ARVC based on a few minor criteria. She cannot undergo a cardiac MRI due to significant renal dysfunction. Genetic testing does *not* reveal any relevant mutations. You consider endomyocardial biopsy. Which of the following statements is *incorrect* about the use of endomyocardial biopsy in patients with suspected ARVC?
- A. The loss of normal RV myocardium with evidence of fibrofatty infiltration supports the diagnosis
 - B. The risk of cardiac perforation is equivalent for RV septal wall and RV free wall biopsies
 - C. RV septal wall or LV biopsies are not usually helpful
 - D. There is a high rate of false negatives and low sensitivity
 - E. The diagnostic yield may be improved by using electroanatomic voltage mapping to guide biopsy
- 62-8.** You refer your patient with probable ARVC to a specialized center for genetic testing. Which of the following statements is *incorrect*?
- A. The predominant inheritance pattern is autosomal recessive with variable penetrance and expressivity, although an autosomal dominant pattern has been described
 - B. Class I recommendation for mutation-specific screening of family members following the identification of a pathogenic mutation in the proband
 - C. Class IIa recommendation for genetic testing of confirmed cases of ARVC
 - D. Class IIb recommendation for genetic testing of borderline cases of ARVC
 - E. Class III recommendation for genetic testing of patients who fulfill only a single minor Task Force criterion
- 62-9.** All of the following put a clinically confirmed ARVC patient at a higher risk for sudden cardiac death *except*:
- A. Unexplained syncope
 - B. Older age
 - C. Left ventricular dysfunction
 - D. Presence of heart failure
 - E. Sustained ventricular arrhythmias
- 62-10.** A 25-year-old man presents with frequent premature ventricular contractions (PVCs). Twenty-four-hour Holter monitoring reveals a PVC burden of 18%. The morphology of the PVCs is consistent with a left bundle branch pattern with a transition at V5, with an inferior axis suggesting an origin at the right ventricular outflow tract (RVOT). Which of the following is more suggestive of ARVC as opposed to RVOT-ventricular tachycardia (VT)?
- A. Good response to verapamil
 - B. Endocardial ablation suppresses the arrhythmia
 - C. RVOT-VT is difficult to induce by programmed ventricular stimulation
 - D. QRS duration during VT is shorter (< 120 ms in lead I)
 - E. A single VT morphology with LBBB pattern and an inferior axis is commonly recorded

ANSWERS

- 62-1. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 62*) Inverted T waves in the right precordial leads must be present past V2 to constitute a major criterion: including V1, V2, and V3 or beyond in patients > 14 years of age in the absence of complete right bundle branch block. Otherwise, inverted T waves in leads V1 and V2 only is a *minor* finding. Originally dating back to 1994, the Task Force criteria for ARVC were modified in 2010 to improve the diagnosis and management of ARVC. The criteria were aimed at facilitating the recognition and interpretation of the clinical and pathologic features of ARVC, and the modified criteria incorporated new knowledge on the genetic basis of the disease, improving diagnostic sensitivity and maintaining diagnostic specificity. The structural, histologic, ECG, arrhythmic, and genetic features are structured in major and minor criteria. The Task Force document formally introduced the

biventricular variant and the left dominant variant.¹ Options A and C through E represent major criteria from the updated Task Force criteria. A definite diagnosis requires two major, or one major and two minor, or four minor criteria from different categories to be fulfilled.

- 62-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 62*) The prevalence of ARVC is estimated to range from 1 in 1000 to 1 in 5000 in the general population.²⁻⁵ A small proportion of patients progress to LV dysfunction; in these patients, the clinical hallmark remains ventricular arrhythmias.⁶ The prevalence of clinical manifestations of the disease is higher in males than in females (3:1).⁷⁻⁸ The disease usually manifests in young adults; of 439 index patients described by Groeneweg et al,⁷ only 4 presented before the age of 13 years, while none presented before the age of 10 years. The reason could be related to the completion of intercalated disk maturation or the need for prolonged exposure to exercise before the disease becomes manifest.⁷
- 62-3. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 62*) Intercalated disks are highly specialized cell-cell junctions; they are the units of electromechanical continuity between cardiac myocytes (option A)⁹ and are constituted of gap junctions (option C), adherens junctions (option D), and desmosomes (option E). In *dilated* cardiomyopathy, genetic abnormalities in the sarcomere may be causal for disease (option B). *Gap junctions* (nexus, communicating junctions) are located in the lateral parts of the intercalated disks and mediate ionic traffic between the adjacent cells and provide the basis for functional cell coupling. Key structural proteins are connexins; the connexins predominantly expressed by cardiac myocytes are Cx43, Cx40, and Cx45. *Adherens junctions* (fasciae adhaerentes) are located in the transverse parts of the intercalated disks where the actin filaments of the sarcomeres are anchored and connected with the plasma membrane. This anchorage provides the intercellular “mechanical continuity” between the myocytes supporting the transmission of force between cells and synchronous contraction and relaxation. *Desmosomes* (maculae adhaerentes) are located in both the transverse and lateral parts of the intercalated disks: they reinforce the adherens junctions and fix adjacent cells. Desmosomes bind desmin on the intracellular side, span the cell membrane, and bind adjacent desmosomes on the extracellular side. Desmosome-forming proteins include plakophilin-2 (PKP2), desmoglein 2 (DSG2), desmocollin 2 (DSC2), plakoglobin (JUP), and desmoplakin (DSP).
- 62-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 62*) It is relatively uncommon for patients with ARVC to present with symptoms of right heart failure. Those with ARVC typically present between the second and fifth decades of life.¹⁰ Symptoms are heterogeneous but most commonly reflect the presence of ventricular arrhythmias, which can range from isolated premature ventricular contractions to sustained ventricular tachycardia. Supraventricular arrhythmias also occur in 14% of ARVC patients, with atrial fibrillation being the most frequently reported.¹¹ In a study of 129 probands, symptoms on presentation included palpitations in 56%, dizziness in 29%, syncope in 26%, chest pain in 19%, and cardiac arrest in 22%.¹² Symptoms related to right heart failure are present in 6% (option A).¹³ These findings are consistent with other studies.^{4,10,14-15}
- 62-5. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 62*) Naxos disease (option B) and Carvajal syndrome (option E) are distinctive forms of ARVC that are inherited in an autosomal recessive manner in association with extracardiac manifestations, including wooly hair and plantopalmar keratoderma (thickening of the skin on the palms and soles).¹⁶ Carvajal syndrome is a variant of Naxos disease with predominant LV involvement (option E) as noted in the question stem. Premature ventricular contractions with a right bundle branch morphology typically originate from the left ventricle, and with a superior axis and negativity in lead I they suggest an anterolateral LV origin. Anderson–Tawil syndrome, or long QT type 7 (option A), is characterized by periodic paralysis, ventricular arrhythmias, and prolonged QT interval (specifically polymorphic ventricular tachycardia and premature ventricular contractions), and anomalies including low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. Brugada syndrome (option C) can mimic ARVC because both conditions may demonstrate RV conduction delay, and mutations typically recurrent in Brugada syndrome have been found in ARVC patients and vice versa. The demonstration of the presence of structural abnormalities supports the diagnosis of ARVC. Catecholaminergic polymorphic ventricular tachycardia (option D) is another inherited arrhythmia characterized by episodic syncope that occurs during exercise or acute emotion in individuals without structural cardiac abnormalities; the underlying cause is the onset of fast ventricular tachycardia (bidirectional or polymorphic).
- 62-6. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 62*) The triangle of dysplasia involves the epicardial subtricuspid region, RV basal anterior wall, and posterolateral LV, with the RV apex being mostly spared.¹⁷ Historically, the *triangle of dysplasia* referred to the RV apex, the RV inflow tract, and the outflow tract and was thought only to be present in advanced stages of the disease.¹⁷⁻¹⁸ Although cardiac MRI has emerged as the preferred imaging modality for ARVC, it is also one of the most common reasons for misdiagnosis. Common pitfalls include misinterpretation of variants of normal RV wall motion and inaccurate interpretation of intramyocardial fat infiltration.¹⁹ It is important to note that in pediatric ARVC patients, intramyocardial fat infiltration and myocardial fibrosis are uncommon findings by CMRI.²⁰
- 62-7. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 62*) An increased risk of cardiac perforation and tamponade is present with a biopsy at the RV free wall. Endomyocardial biopsy is rarely performed but may be helpful in establishing a diagnosis of ARVC when the etiology of cardiomyopathy or structural changes are unclear. The American College of Cardiology/American Heart Association consensus guidelines give a Class IIa (level of evidence C) indication for

endomyocardial biopsy in patients with heart failure when a specific diagnosis is suspected that would influence therapy.²¹ The demonstration of fibrofatty infiltration with loss of normal RV myocardium supports the diagnosis (option A).²²⁻²³ There is a high rate of false negatives and low sensitivity as a result of the patchy nature of disease and the predilection for specific areas of the RV (option D).²³ Thus, conventional RV septal wall or LV biopsies are not helpful because these areas are commonly spared. Diagnostic yield may be improved by using electroanatomic voltage mapping to guide biopsy (option E).²⁴

- 62-8. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 62*) The predominant inheritance pattern is autosomal dominant with variable penetrance and expressivity, although an autosomal recessive inheritance pattern has been described with the cardiocutaneous syndromes of Naxos disease and Carvajal syndrome (option A).¹⁶ Approximately 60% of probands will have an identifiable pathogenic mutation.⁷ Identification of a pathogenic mutation on genetic testing is a major criterion for the diagnosis of ARVC.²² Currently, one of the major roles of genetic testing in ACM is for mutation-specific screening of family members following the identification of a pathogenic mutation in the proband (option B). The Heart Rhythm Society and European Heart Rhythm Association expert consensus guidelines give this indication a Class I recommendation.²⁵ Although genetic testing may be useful for confirmed cases (Class IIa)(option C) or considered for borderline cases (Class IIb)(option D), it is not recommended (Class III)(option E) for those fulfilling only a single minor Task Force criterion.²⁵ The clinical genetic and molecular workup in the proband and his or her family should be performed as in other familial cardiomyopathies and include clinical and genetic screening of first-degree relatives. A positive family history of ARVC is a risk factor for disease, with over a third of family members of affected individuals developing disease.^{7,26-27} The cumulative 5-year and 10-year probabilities of developing ARVC in first-degree family members are 7% and 21%, respectively, with siblings of probands having a threefold higher risk compared to parents or children.²⁶ Pathogenic mutations are identified in 36% to 72% of selected family members, and up to 40% of these individuals will fulfill Task Force criteria for ARVC.^{7,28} Disease will still occur in 18% of those who are mutation negative.⁷ Also, the presence of symptoms or the occurrence of more than one genetic variant in family members increases the likelihood of Task Force criteria–confirmed disease.^{7,26,28} The constellation of findings highlights the complexity of the genetics of ARVC and firmly supports the screening of family members of affected individuals.
- 62-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 62*) There are no prospective, randomized clinical trials to identify who has the highest risk for sudden cardiac death (SCD) and would benefit most from an implantable cardioverter-defibrillator (ICD). However, based on observational studies in ARVC patients, a history of prior cardiac arrest, sustained ventricular arrhythmias (option E), unexplained syncope (option A), *younger* age (option B), extensive RV dysfunction, LV dysfunction (option C), and the presence of heart failure (option D) are independently associated with subsequent ventricular arrhythmias.²⁹⁻³⁷ In a study of patients receiving ICDs for definite or probable ARVC, 48% received an appropriate ICD therapy during a mean follow-up of 5 years.³⁸ The only independent predictors of ICD therapy were the presence of nonsustained VT and inducibility at electrophysiology study. The role of electrophysiology study for risk stratification is unclear because studies provide conflicting evidence.^{31,33,38,39}
- 62-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 62*) Differential diagnoses of ARVC include idiopathic RV outflow tract VT (RVOT-VT), sarcoidosis, myocarditis, dilated cardiomyopathy, Brugada syndrome, athlete's heart, RV infarction, Chagas disease in endemic areas, pulmonary hypertension, and congenital heart disease. Idiopathic RVOT-VT should be differentiated from early ARVC, when gross structural abnormalities are absent. Differential diagnosis is based on clinical data (Task Force criteria), pathology data (endomyocardial biopsy), and imaging data such as echocardiography and cardiac MRI or positron emission tomography demonstrating or excluding scars and inflammation.^{40,41} In general, in RVOT-VT: (1) Twelve-lead surface ECG and SAEKG are normal during sinus rhythm, (2) A single VT morphology with LBBB pattern and an inferior axis is commonly recorded (option E),⁴² (3) QRS duration during VT is *longer* (≥ 120 ms in lead I) (option D),⁴³ (4) a notched QRS and precordial transition in lead V6 recur in ARVC but not in RVOT-VT,⁴⁴ (5) RVOT-VT is difficult to induce by programmed ventricular stimulation (option C),⁴¹ (6) patients with idiopathic RVOT-VT are good responders to verapamil (option A),⁴¹ and (7) endocardial ablation suppresses the arrhythmia in RVOT-VT (option B).⁴¹

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CHAPTER 63

Myocarditis

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 63-1.** A 42-year-old man presents with two weeks of dyspnea on exertion, pedal edema, and orthopnea. One month ago, he had a mild febrile illness. Echocardiography confirms reduced left ventricular (LV) systolic dysfunction. Serologies are suggestive of a viral myocarditis secondary to coxsackievirus B3. Which of the following is *not true* regarding coxsackie-mediated viral myocarditis?
- A. Myocardial infection is initiated by the transmembrane coxsackievirus-adenovirus receptor (CAR)
 - B. Cell damage is induced by direct cytotoxicity and is mediated by viral proteinases
 - C. Patients with defects of dystrophin and dysferlin demonstrate increased susceptibility to myocardial CV-B3 infection
 - D. The early innate immune response results in direct myocyte injury
 - E. All of the above are true
- 63-2.** Which of the following is *not* associated with a poor outcome after a diagnosis of viral myocarditis?
- A. New York Heart Association (NYHA) classes III to IV symptoms at 6 months
 - B. Biventricular dysfunction at the time of diagnosis
 - C. The presence of late gadolinium enhancement (LGE)
 - D. High rate of cardiomyocyte apoptosis on biopsy
 - E. Presentation with heart failure symptoms
- 63-3.** A 67-year-old woman received an orthotopic heart transplant 6 months ago. She presents with generalized malaise and new-onset heart failure. Echocardiography confirms allograft dysfunction, and serum PCR demonstrates human cytomegalovirus (HCMV) viremia. Which of the following is *true* regarding HCMV myocarditis?
- A. Myocardial infection with HCMV is usually observed in immunocompetent hosts
 - B. Myocardial pathology is notable for an infiltrate by eosinophils
 - C. Viral infection is restricted to myocytes
 - D. In immunosuppressed patients, infection often occurs by reactivation of a latent infection
 - E. First-line treatment is with acyclovir
- 63-4.** A 43-year-old woman presents with new-onset heart failure, generalized myalgias, and periorbital swelling. A careful history indicates that she has a predilection for eating raw pork. Which of the following is *not true* regarding *Trichinella* myocarditis?
- A. Infection of striated muscles occurs in the first phase of infection
 - B. A complete blood count can show hypereosinophilia
 - C. A muscle biopsy would show larvae
 - D. Treatment is albendazole
 - E. All of the above
- 63-5.** Which of the following is *true* of cardiac MRI (CMR) findings of acute myocarditis?
- A. CMR findings are diagnostic but not prognostic
 - B. LGE is present in a noncoronary distribution
 - C. CMR would show decreased myocardial edema
 - D. Early gadolinium enhancement is normal
 - E. The presence of a pericardial effusion increases the diagnostic accuracy of CMR for myocarditis
- 63-6.** A 20-year-old college student presents with acute decompensated heart failure. His history is notable for a recent study

abroad in South America. Which of the following is *true* for Chagas myocarditis?

- A. The causal agent is *T. gondii*
- B. Myocarditis is part of the acute phase
- C. The chronic phase can lead to chronic cardiomyopathy
- D. Treatment is with trimethoprim-sulfamethoxazole
- E. Both B and C are correct

63-7. A 48-year-old woman from Wisconsin presents with syncopal episodes. Approximately three weeks earlier she had been camping and noted a bulls-eye rash. Which of the following is *true* of Lyme carditis?

- A. Lyme carditis typically manifests at the same time as erythema migrans
- B. Atrioventricular block can occur within a week of infection
- C. Patients often recall erythema migrans at the time of presentation
- D. Myopericarditis results in focal wall motion abnormalities
- E. Both A and D are correct

63-8. A 38-year-old man presents with acute cardiogenic shock and incessant ventricular arrhythmias. After he is stabilized with mechanic circulatory support, an endomyocardial biopsy is performed. The results are shown in [Figure 63-1](#). Which of the following is *true* of this condition?

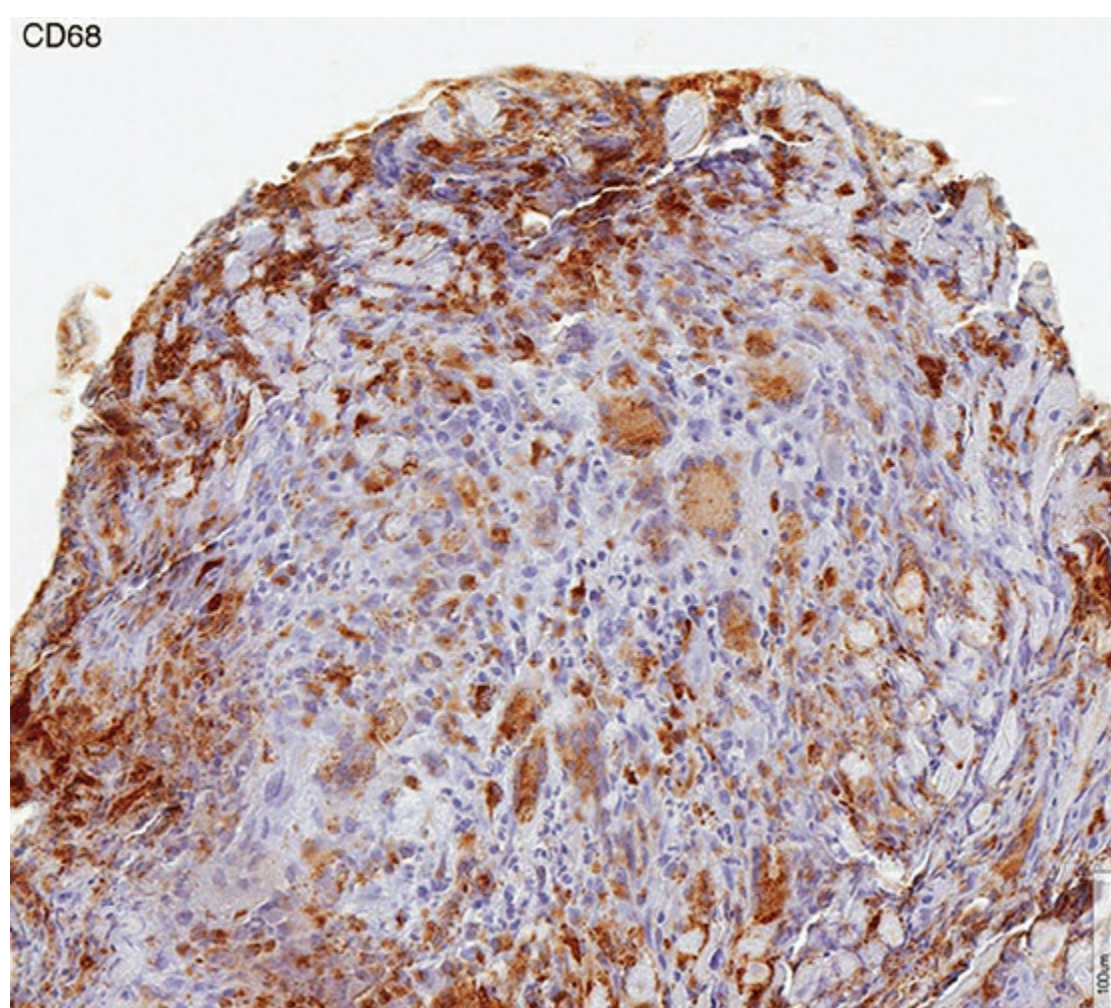


FIGURE 63-1 Biopsy from patient in question 63-8 after staining with anti-CD68.

- A. The prognosis is excellent
- B. Treatment with muromonab-CD3 may be of benefit
- C. Following transplantation, recurrence in the donor heart can occur
- D. Mechanical support often requires biventricular support
- E. Both C and D are correct

63-9. A 47-year-old woman presents with wheezing and syncope. A chest x-ray shows hilar lymphadenopathy, and an echocardiogram reveals left ventricular dysfunction. Which of the following is *not true* about sarcoidosis?

- A. The pathologic hallmark is noncaseating epithelioid granulomas in the affected tissues
- B. Endomyocardial biopsy is both sensitive and specific for diagnosing cardiac sarcoidosis
- C. Patients with cardiac sarcoid and normal LV ejection fraction (LVEF) continue to be at risk for arrhythmia
- D. LGE by cardiac MRI corresponds with biopsy findings of granuloma
- E. Cardiac PET can be used to assess arrhythmogenic risk

63-10. Which of the following is *true* of cardiac involvement with hypereosinophilic syndrome (HES)?

- A. Affected patients often present with acute decompensated heart failure during the acute necrotic stage
- B. During the thrombotic phase, oral anticoagulation is appropriate to prevent major embolic events
- C. Late cardiac involvement results in a restrictive cardiomyopathy
- D. Both B and C are true

E. All of the above

ANSWERS

- 63-1. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 63*) The cardiotropic coxsackievirus B3 (CV-B3) is one of the most common causes of myocarditis.¹ The myocardial infection is initiated by the transmembrane CAR; the ablation of CAR blocks viral affliction of myocardial cells and inflammation in the myocardium in experimental models (option A).² In CV-B3–infected myocytes, the cell damage is induced by direct cytotoxicity and mediated by viral proteinases (option B).³ Patients with defects of dystrophin and dysferlin demonstrate increased susceptibility to myocardial CV-B3 infection by enhancing viral propagation to adjacent cardiomyocytes and disrupting membrane repair function (option C).⁴⁻⁶ In viral infections, the early innate immune response provides the first defense mechanism and is mediated by cytokines. However, the late adaptive immune response contributes to the myocardial lymphocyte infiltration that must clear virus-infected cardiac myocytes in CV-B3 myocarditis and endothelial cells in parvovirus B19 myocarditis. Although this mechanism clears the virus, it also results in myocyte injury (option D).
- 63-2. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Predictors of outcome vary in different myocardial biopsy studies. Persistence of New York Heart Association (NYHA) classes III to IV, left atrium enlargement, and improvement in LVEF at 6 months emerged as independent predictors of long-term outcome in one study (option A).⁷ Biventricular dysfunction at diagnosis was the main predictor of death/transplantation in another study (option B).⁸ High rates of cardiomyocyte apoptosis were associated with functional recovery at 1 year (option D).⁹ The presence of LGE emerged as the best independent predictor of all-cause and cardiac mortality, whereas the initial presentation with heart failure was a predictor of incomplete long-term recovery (options C and E).¹⁰
- 63-3. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Myocardial infection with HCMV is more commonly observed in immunocompromised hosts (option A). The myocardial pathology is characterized by T-cell inflammatory infiltrate and by the presence of typical intranuclear amphophilic inclusion bodies that specifically immune-stain with anti-HCMV antibodies (option B). The virus infects both myocytes and endothelial cells (option C). Children become infected early in life in developing countries, whereas up to 80% of the adult population is infected in developed nations. The course of primary infection is usually mild or asymptomatic in immunocompetent hosts as HCMV establishes a latent but persistent infection reflecting the inability of the immune system to clear the infection; immune evasion mechanisms allow infected cells to escape both innate and adaptive effector immunity.¹¹ In immunosuppressed patients (eg, solid organ or bone marrow transplantation recipients), the infection can be reactivated to result in systemic and organ infection; the heart is a possible target for tissue infection, especially in heart transplant recipients (option D). For herpes simplex virus types 1 and 2 and for varicella-zoster virus, acyclovir (or its prodrug valacyclovir) and famciclovir have greatly reduced the burden of disease and have demonstrated a remarkable safety record. Ganciclovir and valganciclovir remain the drugs of choice for HCMV infection in immunocompromised hosts (option E).^{12,13}
- 63-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Eosinophilic myocarditis is a possible complication in patients with trichinosis, a zoonosis caused by nematodes of the genus *Trichinella*. *Trichinella* is endemic in the areas with unregulated slaughter of pigs and particularly in areas where these are in contact with wild animals.^{14,15} Symptoms of trichinosis occur in two stages. Intestinal infection is the first stage and develops 1 to 2 days after consuming contaminated meat. The most common symptoms are nausea, diarrhea, abdominal cramps, and fever. The second stage corresponds to larval invasion of muscles and starts after about 7 to 15 days (option A). The diagnosis of trichinellosis should be based on clinical findings; pathology findings of muscle and/or EMB detecting larvae; laboratory findings of specific antibody response by indirect immunofluorescence, ELISA, or Western blot; hypereosinophilia (1000 eosinophils/mL) and/or increased total IgE levels; increased levels of muscle enzymes; and investigation of the possible source and origin of infection (options B and C).¹⁴⁻¹⁶ When the diagnosis is proven, the treatment is based on antihelminthic drugs, such as albendazole or mebendazole, and supportive therapy in patients with heart failure (option D).¹⁵
- 63-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 63*) CMR provides a detailed morphofunctional description of ventricular involvement and offers important prognostic information.¹⁷ There is a substantially lower risk of events in patients with suspected myocarditis but normal CMR findings (option A).¹⁸ According to the Lake Louise CMR criteria, acute myocarditis is associated with (1) increased regional or global myocardial signal intensity in T2-weighted images (indicating myocardial edema); (2) increased global myocardial early gadolinium enhancement (EGE) ratio between myocardium and skeletal muscle in T1-weighted images (supporting hyperemia/capillary leakage); and (3) at least one focal lesion with nonischemic distribution in LGE T1-weighted images (suggestive of cell injury/necrosis) (options B through D).¹⁷ The diagnostic accuracy does not increase with the addition of pericardial effusion (option E).¹⁹
- 63-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Chagas disease (CD) is caused by the protozoan parasite

T. cruzi (option A).²⁰ In the acute phase, the disease can manifest with myocarditis, conduction system abnormalities, and pericarditis (option B). In untreated patients, the disease progresses to the chronic phase.^{21,22} In the chronic phase, illness can be severe, with LV dilation and dysfunction, aneurysm, congestive heart failure, thromboembolism, ventricular arrhythmias, and sudden cardiac death, which is the leading cause of death in patients with Chagas heart disease (option C).²³ Two antiparasitic drugs are available for the treatment of CD: benznidazole and nifurtimox (option D).^{23,24}

- 63-7. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Lyme carditis is rare and typically manifests 2 to 5 weeks after the erythema migrans (option A). Patients who develop Lyme disease may first manifest atrioventricular block at 14 days (range, 2–24 days) after the onset; only one-third of patients recall the erythema migrans (options B and C).^{25,26} Myopericarditis can present with chest pain, dyspnea, or syncope, and the signs and symptoms of Lyme myopericarditis can mimic acute coronary syndrome, with ECG ST-segment alterations and elevated peripheral blood cardiac biomarkers.²⁶ In such cases, echocardiography demonstrates diffuse ventricular hypokinesis rather than the focal wall motion abnormalities expected with an acute coronary syndrome (option D).²⁵
- 63-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 63*). The biopsy in [Figure 63-1](#) shows giant cells consistent with a diagnosis of giant cell myocarditis. GCM carries a poor prognosis, with a median survival of 5.5 months from the onset of symptoms; in one report, 89% of patients either died or required cardiac transplantation, and another report showed 1-year survival of 30% to 69% (option A).^{27,28} Mechanical circulatory support for bridge to recovery is rare, whereas it is more commonly used as bridge to transplant; biventricular support is often required (option D).^{29,30} Heart failure treatment includes standard regimen with beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists as per guidelines.^{31,32} The management of GCM has also included the use of muromonab-CD3, pulse steroids, and varying combinations of azathioprine, cyclosporine, and prednisone monitored with surveillance EMB (option B). Post-transplant survival is similar to that of patients who underwent heart transplantation for other diseases; however, GCM may recur in 10% to 50% of transplanted hearts (option C).^{27,28,33}
- 63-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Sarcoidosis is a chronic multisystem inflammatory disease of unknown etiology that carries the pathologic hallmark of noncaseating epithelioid granulomas in the affected tissues (option A).³⁴ CMR offers a high sensitivity and specificity for the assessment of cardiac involvement. Whereas T2 hyper-enhancement identifies early edema, the LGE in a nonvascular distribution supports myocardial scarring. LGE correlates with cardiac biopsy findings of granulomatous inflammation (option D).^{35,36} In patients with preserved LVEF and extracardiac sarcoidosis, major adverse cardiac events, including death and ventricular tachycardia, are associated with a greater LGE and right ventricular involvement; preserved LVEF does not exclude the risk for adverse events (option C).³⁷ Additionally, PET studies have proved to be clinically useful for diagnostic and prognostic information, especially for the risk of ventricular arrhythmias in patients with cardiac sarcoidosis. The presence of focal perfusion defects (rubidium-82 imaging in this report) and FDG uptake identified a higher risk of death or ventricular tachycardia (option E).³⁸ Although EMB has low sensitivity (19%–32%) as a result of the inherent sampling limitation for focal epithelioid granulomas, it offers high specificity for the diagnosis (option B).³⁹
- 63-10. The answer is D.** (*Hurst's The Heart, 14th Edition, Chap. 63*) Cardiac involvement is a major cause of morbidity and mortality in HES.⁴⁰ The cardiac pathology is divided into three stages: (1) an acute necrotic stage, (2) a thrombotic stage, and (3) a fibrotic stage. The early, acute necrotic stage is characterized by eosinophilic and lymphocyte infiltration; in the myocardial interstitium, eosinophils undergo degranulation with release of biologically active factors that cause myocyte injury. Clinical presentation may comprise nonspecific manifestations. Patients may *infrequently* present with acute heart failure or cardiogenic shock at onset (option A).⁴¹ In the thrombotic stage, mural thrombi develop on the endocardium. Thromboembolic complications occur in up to 30% of patients; oral anticoagulation is appropriate to prevent major embolic events (option B). In the scarring, fibrotic stage, both ventricles and subvalvular structures of the AV valves are involved. The functional phenotype is typically restrictive as in endomyocardial fibrosis (option C).

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CHAPTER 64

The Athlete and the Cardiovascular System

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 64-1.** A 56-year-old woman presents for an exercise stress test. She completes 10.2 METS. The acute response to aerobic exercise includes increases in all of the following *except*:
- A. Maximum oxygen consumption
 - B. Cardiac output
 - C. Stroke volume
 - D. Systolic blood pressure
 - E. Peripheral vascular resistance
- 64-2.** A 29-year-old professional athlete is referred to you with left ventricle (LV) hypertrophy on his echocardiogram. Which criteria favor hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy over the athletic heart syndrome?
- A. LV wall thickness ≥ 16 mm
 - B. LV hypertrophy with an unusual distribution (heterogeneous, asymmetric, or sparing the anterior septum)
 - C. Persistence of hypertrophy after physical deconditioning
 - D. LV end-diastolic diameter > 70 mm
 - E. All of the above
- 64-3.** A 29-year-old Olympic canoeist is referred to you by her family physician with an abnormal ECG pattern. Which ECG abnormality is *not* commonly seen on the ECGs of elite endurance athletes?
- A. Incomplete left bundle branch block
 - B. Early repolarization
 - C. Increased QRS voltages with diffuse T-wave inversion and deep Q waves
 - D. Mildly increased P-wave amplitude
 - E. Increased voltages consistent with right ventricular and LV hypertrophy
- 64-4.** An endurance runner is referred to you by his family physician after a routine ECG shows an arrhythmia. Which of the following arrhythmias are *not* commonly noted among elite athletes?
- A. Sinus arrhythmia and sinus bradycardia
 - B. First-degree and Mobitz type II second-degree AV block
 - C. Frequent premature beats and couplets
 - D. Nonsustained ventricular tachycardia
 - E. Junctional rhythm
- 64-5.** A 22-year-old college football player has a cardiac arrest and sudden death during a championship game. Which of the following statements is *not true* about sudden death in athletes?
- A. Sudden death occurs with an incidence of 1 to 2 per 100,000 athletes (12 to 35 years of age) per year
 - B. The frequency of sudden death is fourfold lower in female athletes
 - C. In athletes younger than 35 years, inherited diseases such as HCM, arrhythmogenic right ventricular cardiomyopathy, and congenital coronary artery abnormalities of wrong sinus origin are the most common causes of sudden death
 - D. In athletes older than 35 years, atherosclerotic coronary artery disease is the most common cause of death
 - E. All of the above are true
- 64-6.** A 17-year-old athlete is referred to you for assessment after a cardiac arrest requiring resuscitation during a high school basketball game. Which of the following statements is *true* about HCM?

- A. HCM is the single most common cause of sudden cardiac arrest in athletes in the United States
- B. HCM accounts for about one-third of sport-related sudden fatalities
- C. HCM is a genetically transmitted disease characterized by genotypic and phenotypic heterogeneity
- D. LV hypertrophy is characteristically asymmetric with a variety of patterns of wall thickening
- E. All of the above are true

64-7. Which of the following statements is *not true* regarding arrhythmogenic right ventricular cardiomyopathy?

- A. Arrhythmogenic right ventricular cardiomyopathy is an inherited heart muscle disorder characterized pathologically by fibrofatty replacement of right ventricular myocardium
- B. It is an uncommon cause of sudden death on the athletic field in the United States
- C. Clinical manifestations include ECG depolarization and repolarization abnormalities commonly localized to right precordial leads
- D. Myocardial aneurysms are localized to the posterobasal, apical, and outflow tract regions
- E. Sudden death during physical exercise is likely related to hemodynamic factors, increased right ventricular volume and wall stress, and enhanced sympathetic tone that culminate in ventricular fibrillation

64-8. A 15-year-old lacrosse player who recently had a normal history and physical with his family physician collapses during a game. Which of the following statements is *true* regarding sudden death in athletes with no evidence of structural heart disease?

- A. Approximately 10% of young athletes who die suddenly with exercise have no evidence of structural heart diseases
- B. Sudden death may be due to ventricular pre-excitation
- C. Sudden death may be due to inherited cardiac ion channelopathies, including long QT syndrome, short QT syndrome, and Brugada syndrome
- D. Sudden death may be due to catecholaminergic polymorphic ventricular tachycardia
- E. All of the above are true

64-9. An amateur boxer collapses shortly after being punched in the chest. Which of the following statements is *not true* about commotio cordis?

- A. The most common sports associated with commotio cordis deaths in the United States are those in which projectiles are integral to the game
- B. Collapse is almost never instantaneous and is usually delayed to 10 to 20 seconds after the chest blow
- C. The most common cardiac arrhythmia documented soon after collapse is generally ventricular fibrillation
- D. Survival from commotion cordis has increased to > 50% as a result of more rapid response times and access to external defibrillation as well as greater public awareness
- E. The cellular determinants of VF induced by chest wall blows likely include ion channel activation caused by increased LV pressure

64-10. Which of the following is *not true* with respect to the routine use of ECGs during athlete screening in the United States?

- A. Routine use of ECG screening has not been supported because of the large number of athletes to be screened
- B. Routine use of ECG screening has not been supported because of the low incidence of events
- C. Routine use of ECG screening has not been supported because of the substantial number of expected false-negative and false-positive results
- D. Routine use of ECG screening has not been supported because of the need for repetitive ECG screening during adolescence
- E. Routine use of ECGs is mandated as part of athlete screening in the United States

ANSWERS

64-1. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 64*) The acute response to training for such athletic activities as cross-country skiing, long-distance running, swimming, or bicycling includes substantial increases in maximum oxygen consumption (option A), cardiac output (option B), stroke volume (option C), and systolic blood pressure (option D), associated with decreased (*not increased*) peripheral vascular resistance (option E).¹ With several weeks of endurance training, the chronic adaptations to training include increased maximal oxygen uptake from augmented stroke volume and cardiac output and increased arteriovenous oxygen difference. The response to endurance exercise predominantly produces a volume load on the left ventricle.

64-2. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 64*) Differentiating the physiologic changes resulting from habitual exercise in the athletic heart syndrome with HCM or dilated cardiomyopathy represents a challenge to the clinician. Physiologic cardiac adaptation from regular exercise leads to an increase in left ventricle (LV) wall thickness.

This can be difficult to distinguish from the pathologic changes of HCM. Criteria favoring HCM include a high degree of LV hypertrophy (wall thickness ≥ 16 mm) (option A) with an unusual distribution (heterogeneous, asymmetric, or sparing the anterior septum) (option B), a small LV cavity (< 45 mm), the presence of striking electrocardiogram (ECG) abnormalities, and the persistence of hypertrophy after physical deconditioning (option C). Although many athletes have increased intracavitary dimensions, LV end-diastolic diameter > 70 mm is distinctly unusual as a manifestation of the athlete's heart (option D). LV wall thickness > 12 mm is unusual even in highly trained athletes but is not uncommon in elite rowers and cyclists. LV wall thickness ≥ 16 mm raises the possibility of HCM. Hypertrophy (> 12 mm) above the normal range is distinctly uncommon in female athletes. Athletes with LV wall hypertrophy may have increased cavity dimensions, which are rarely present in diseases with pathologic wall thickening.¹

- 64-3. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 64*) A spectrum of abnormal 12-lead ECG patterns is present in up to one-half of trained athletes, more commonly in men and in endurance athletes.²⁻⁷ The most commonly observed alterations include early repolarization patterns (option B), increased QRS voltages, diffuse T-wave inversion, and deep Q waves (option C). ECGs in endurance athletes can show mildly increased P-wave amplitude (option D), suggesting atrial enlargement, incomplete right (*not left*) bundle branch block (option E), and increased voltages consistent with right ventricular and LV hypertrophy.²⁻⁷ Among endurance athletes, voltage criteria for right ventricular hypertrophy are present in a substantial proportion. Abnormal and bizarre ECG patterns suggestive of cardiac disease are noted in a minority of elite athletes.²⁻⁷ Most such ECGs represent only extreme manifestations of physiologic athlete's heart. A significant minority of asymptomatic elite athletes show distinctly abnormal ECG patterns usually associated with precordial T-wave inversions but without evidence of cardiac disease.⁸ Many uncommon ECG findings in athletes are not considered normal variants and require further evaluation.
- 64-4. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 64*) Arrhythmias commonly noted in athletes include sinus arrhythmia, sinus bradycardia (option A), and junctional rhythm (option E). They are often accompanied by other manifestations of enhanced parasympathetic tone. Atrioventricular (AV) conduction delays with first-degree and Wenckebach or Mobitz type I (*not Mobitz type II*) second-degree AV block (option B) are common in endurance athletes and attributable to enhanced vagal tone and withdrawal of sympathetic tone at rest.⁸ Ambulatory monitoring of athletes has demonstrated ventricular arrhythmias, including frequent premature beats, couplets (option C), and nonsustained ventricular tachycardia (option D). These arrhythmias can be within the spectrum of physiologic athlete's heart.⁸ Such arrhythmias are generally not associated with symptoms or an increased risk of sudden cardiac death, and they are generally reduced with exercise or deconditioning.⁹
- 64-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 64*) The underlying cardiovascular conditions that predispose to the rare and tragic sudden deaths in young athletes are known.¹⁰⁻¹⁶ Available population-based data show that these events occur with an incidence of 1 to 2 per 100,000 athletes (12–35 years of age) per year (option A) with the frequency eightfold lower (*not fourfold lower*) in female athletes (option B).¹⁰⁻¹⁶ In athletes younger than 35 years, inherited diseases such as HCM, arrhythmogenic right ventricular cardiomyopathy, and congenital coronary artery abnormalities of wrong sinus origin are the most common causes of sudden death (option C). In athletes older than 35 years, atherosclerotic coronary artery disease is the most common cause of death (option D).¹⁰⁻¹⁶
- 64-6. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 64*) Hypertrophic cardiomyopathy is the single most common cause of sudden cardiac arrest in athletes in the United States in which a definitive cardiac diagnosis can be made postmortem (option A). HCM accounts for about one-third of sport-related sudden fatalities (option B).¹⁰⁻¹⁶ HCM is a genetically transmitted disease characterized by genotypic and phenotypic heterogeneity (option C). Usually, the characteristic hypertrophied, nondilated LV with increased wall thickness manifests during adolescence.¹⁰ LV hypertrophy is characteristically asymmetric with a variety of patterns of wall thickening (option D).¹⁷
- 64-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 64*) Arrhythmogenic right ventricular cardiomyopathy is an inherited heart muscle disorder characterized pathologically by fibrofatty replacement of right ventricular myocardium (option A).¹⁸⁻²² It represents the leading cause of sudden death on the athletic field in the Veneto region of Italy, accounting for approximately 25% of cardiovascular sudden death in young competitive athletes, but it is distinctly uncommon in the United States (5% of athlete deaths) (option B).¹⁸⁻²² Clinical manifestations include ECG depolarization and repolarization abnormalities commonly localized to right precordial leads (option C). These include inverted T waves in V1-V3 in most patients with arrhythmogenic right ventricular cardiomyopathy. Less commonly, distinctive depolarization waves known as epsilon waves are seen after the QRS complex in the ST segment on the ECG. Cardiac imaging techniques demonstrate right ventricular global or regional morphologic and functional abnormalities.¹⁸⁻²² Commonly, premature ventricular contractions or sustained monomorphic ventricular tachycardia with left bundle morphology originate from the right ventricle and are associated with exercise.¹⁷⁻²² Myocardial aneurysms are localized to the posterobasal, apical, and outflow tract regions (option D), resulting in the clinical characterization of these regions as the triangle of dysplasia. Sudden death during physical exercise is likely related to hemodynamic factors, increased right ventricular volume and wall stress, and enhanced sympathetic tone that culminate in ventricular tachycardia (*not ventricular fibrillation*) (option E).¹⁸⁻²³ Physical exercise can acutely increase right ventricular afterload and cavity enlargement, which in turn can trigger ventricular arrhythmias by stretching the diseased right ventricular musculature.¹⁸⁻²³

- 64-8. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 64*) Approximately 10% of young athletes who die suddenly with exercise have no evidence of structural heart diseases (option A). In many such patients, the cause of sudden death is likely a primary electrical heart disease. These include primary electrical abnormalities such as ventricular pre-excitation (Wolff-Parkinson-White syndrome) (option B) and inherited cardiac ion channelopathies, including long QT syndrome, short QT syndrome, Brugada syndrome (option C), and catecholaminergic polymorphic ventricular tachycardia (option D).²⁴ These primary electrical abnormalities and other conditions predisposing to athletic sudden death have ECG changes.¹⁰⁻¹⁶
- 64-9. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 64*) In the absence of underlying cardiovascular disease, blunt nonpenetrating chest blows²⁵⁻³² during athletic or recreational activities that cause sudden cardiac death are known as commotio cordis. Although first noted a century ago, it is only in the last 15 to 20 years that commotio cordis has been recognized as a not-uncommon occurrence in youth sports, and it is now regarded as the second leading cause of sudden cardiac death in young athletes, with global recognition.²⁵⁻³² The most common sports associated with commotio cordis deaths in the United States are those in which projectiles are integral to the game (eg, baseball, softball, ice hockey, football, lacrosse) (option A). Ages of victims range from 1 to 50 years, although the mean age of individuals experiencing commotio cordis is 14 years, with 30% of individuals older than 18 years. Collapse is *usually instantaneous*, although occasionally delayed 10 to 20 seconds after the chest blow (option B). Cardiac arrhythmias documented soon after collapse are generally ventricular fibrillations (VF) (option C); however, as the time to first documented arrhythmia increases, asystole is more frequently evident. Early reports of resuscitated commotio cordis showed poor survival, although more recently, survival from these events has increased markedly to more than 50% as a result of more rapid response times and access to external defibrillation as well as greater public awareness of this condition (option D).²⁵⁻³² The mechanism by which commotio cordis occurs is complex and largely unresolved, and a porcine model was developed for study of this syndrome, which demonstrated that the immediate cause of collapse was VF.²⁵⁻³² The use of this model has allowed the definition of several important determinants of VF following a chest blow, including, most importantly, an impact delivered directly over the heart and the timing within the vulnerable phase of repolarization (a narrow 10- to 30-millisecond window just prior to the T-wave peak, equivalent to only 1% to 2% of the cardiac cycle) associated with peak LV pressure caused by the blow, although a wide range of individual vulnerability to VF is evident in the model.²⁵⁻³² Furthermore, impact velocity appears to have a Gaussian distribution, with a velocity of 40 mph most likely to trigger VF. In addition, hardness and reduced diameter of the impact object have been correlated directly with the risk of VF.²⁵⁻³² Sudden cardiac death in commotio cordis appears to be a primary electrical event. The cellular determinants of VF induced by chest wall blows likely include ion channel activation caused by increased LV pressure (option E).²⁵⁻²⁹ The potassium–adenosine triphosphate ion channel mediates the initiation of VF in the swine model and has also been shown to be activated by atrial stretch.²⁵⁻²⁹ It is possible that more stretch-activated ion channels are also involved.
- 64-10. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 64*) The routine use of ECGs is *not* mandated as part of athlete screening in the United States (option E). On many occasions, AHA consensus expert panels have evaluated and decided not to support mandatory national athlete screening in the United States with routine use of ECGs.³³⁻³⁶ Indeed, sudden cardiovascular deaths in athletes are rare (albeit tragic) events insufficient in number to be judged as a major public health problem or justify a change in national health care policy. The most frequently cited obstacles to mandatory national screening of trained athletes are: (1) the large number of athletes to be screened nationally on an annual basis (ie, about 10 to 12 million) (option A); (2) the low incidence of events (option B); (3) the substantial number of expected false-negative and false-positive results in the range of 5% to 20%, depending on the specific ECG criteria used (option C); (4) cost-effectiveness considerations (ie, extensive resources and expenses required vs few events in absolute numbers); (5) liability issues for physicians (ie, charged with both enforcement and the sole responsibility for disqualifying athletes from competition); (6) the lack of resources or physicians dedicated to performing examinations and interpreting ECGs, in contrast to the long-standing sports medicine program in Italy; (7) the influence of observer variability, technical considerations, and the impact of ethnicity/race on the interpretation of ECGs, particularly important for multicultural athlete populations such as those in the United States; (8) the need for repetitive (ie, annual) ECG screening during adolescence (option D), given the possibility of developing phenotypic evidence of cardiomyopathies during this time period or later; (9) the logistical challenges and cost related to second-tier confirmatory screening with imaging and other testing, should primary evaluations raise the suspicion of cardiac disease; and (10) the recognition that even with testing, screening cannot be expected to identify all athletes with important cardiovascular abnormalities, and a significant false-negative rate can be expected.³²⁻⁴⁴

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CHAPTER 65

Cardiovascular Disease in the Elderly: Pathophysiology and Clinical Implications

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

65-1. Which of the following is *not* an effect of aging on the gross anatomy of the heart?

- A. Endocardial thickening and sclerosis
- B. Increased left atrial size
- C. Valvular fibrosis and sclerosis
- D. Decreased epicardial fat
- E. All of the above

65-2. Which of the following is a cardiovascular effect associated with aging?

- A. Thrombosis
- B. Bleeding complications with antiplatelet, anticoagulant, and fibrinolytic agents
- C. Sarcopenia
- D. Altered pharmacodynamics
- E. All of the above

65-3. Which of the following statements about multimorbidity is *true*?

- A. The most common pattern of multimorbidity is the coexistence of a cardiometabolic condition and osteoarthritis
- B. The dyad of hypertension and hyperlipidemia is rare among Medicare beneficiaries
- C. Over 50% of Medicare beneficiaries with HF, stroke, or AF have more than seven chronic conditions
- D. Noncardiovascular conditions account for almost a quarter of readmissions after HF or MI in older adults
- E. All of the above

65-4. Which of the following statements about polypharmacy is *false*?

- A. Polypharmacy is defined as concomitant use of three or more medications
- B. About 40% of community-dwelling older adults take at least five medications
- C. About 20% of community-dwelling older adults take medications that may exacerbate coexisting conditions
- D. Medications used to treat arthritis can antagonize the effects of many cardiovascular medications
- E. All of the above

65-5. Which of the following statements about frailty is *false*?

- A. Frailty is characterized by reduced physiologic reserve in multiple organ systems to maintain homeostasis after a stressful event
- B. After functional decline, frailty is considered the second most problematic manifestation of aging
- C. When using a comprehensive definition of frailty, more than 50% of the general population is affected
- D. Persons with three or more criteria from the *frailty phenotype* are considered frail
- E. None of the above statements are false

65-6. Which of the following statements about cognitive impairment is *true*?

- A. Dementia affects 25% of adults age 70 years or older in the United States
- B. The prevalence of dementia increases from 5% in patients age 71 to 79 years to 37% in those over 90 years of age
- C. Mild cognitive impairment is present in 52% of people ≥ 70 years old

- D. The prevalence of cognitive impairment is higher in older adults undergoing CABG than in those who are hospitalized with HF
- E. Large cerebral infarcts, grey matter lesions, lacunes, and microinfarcts are some of the cerebrovascular pathologies associated with dementia

65-7. Which of the following statements is *true* about the effects of aging on the risk of heart failure (HF)?

- A. The high prevalence of HF in elderly patients is *not* solely related to improved survival from acute MI and other CVDs
- B. The exponential rise in HF among older people is due to a gradual erosion in cardiovascular reserve
- C. The effects of normal aging alter the four major determinants of cardiac output
- D. A healthy 90-year-old person has the exercise capacity and cardiovascular reserve equivalent to a younger person with New York Heart Association functional class III HF.
- E. All of the above

65-8. Which of the following statements about the use of intravenous antiplatelet therapy in older adults is *false*?

- A. Patients at a higher risk of reinfarction tend to benefit the most from intravenous antiplatelet therapy
- B. It is difficult to say whether intravenous antiplatelet therapy is beneficial to older adults because few studies have enrolled patients older than 75
- C. Current guidelines recommend avoiding intravenous antiplatelet therapy in STEMI patients ≥ 85 years of age
- D. The use of glycoprotein IIb/IIIa should be limited to older persons with high thrombosis risk and low bleeding risk
- E. All of the above

65-9. Which of the following statements about aortic stenosis (AS) is *true*?

- A. The prevalence of AS in patients older than 80 years of age is higher than 20%
- B. More than 90% of all aortic valve procedures are performed in the geriatric population
- C. AS is an uncommon valvular abnormality in both young and older patients
- D. Symptoms of AS are known to be especially prominent in elderly patients with a sedentary lifestyle
- E. Older individuals with severe AS are less likely to exhibit delayed upstroke of the carotid pulse wave

65-10. Sinus node pacemaker cells degenerate progressively with age. By age 75, approximately what percentage of sinus node pacemaker cells continue to function normally?

- A. 5%
- B. 10%
- C. 20%
- D. 30%
- E. 50%

ANSWERS

65-1. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 65*) The effects of aging on the gross anatomy of the heart are: increased left ventricular wall thickness and decreased cavity size, endocardial thickening and sclerosis (option A), increased left atrial size (option B), valvular fibrosis and sclerosis (option C), and increased (*not decreased*) epicardial fat (option D).

65-2. The answer is E. (*Hurst's The Heart, 14th Edition, Chap. 65*) With increasing age, changes in the hemostatic system shift the intrinsic balance between thrombosis and fibrinolysis in the direction of thrombosis (option A). As a result, older adults are at increased risk for both venous thromboembolic disease (ie, deep venous thrombosis and pulmonary embolism) and thrombosis in the arterial system, including myocardial infarction (MI), left atrial appendage thrombus in AF, and stroke. Despite these changes, and perhaps paradoxically, older adults are also at increased risk for bleeding complications with all antiplatelet, anticoagulant, and fibrinolytic agents (option B), as exemplified by the increased incidence of intracranial hemorrhage in older adults receiving prasugrel or fibrinolytic agents. In addition, age-associated declines in muscular mass (sarcopenia) and bone mass (osteopenia) contribute to reductions in exercise tolerance, adversely affect balance, and predispose to injurious falls (option C). Further, aging is associated with altered pharmacokinetics and pharmacodynamics of almost all medications (option D), so that drug dosages tested in clinical trials involving predominantly younger and healthier patients may not be appropriate for the majority of older adults.

65-3. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 65*) Multimorbidity often involves CVD—the coexistence of a cardiometabolic condition and osteoarthritis was the most common multimorbidity pattern in several population-based studies (option A).¹ Among Medicare beneficiaries, the dyad of hypertension and hyperlipidemia was most prevalent (53%) (option B), and other common conditions were ischemic heart disease, diabetes, and arthritis.^{2,3} In addition, over

50% of Medicare beneficiaries with HF, stroke, or AF have more than five chronic conditions (option C).⁴ Prevalent noncardiovascular conditions include arthritis, anemia, chronic kidney disease, cataracts, chronic obstructive pulmonary disease, dementia, and depression.³ Furthermore, noncardiovascular conditions account for almost half of readmissions after HF or MI in older adults (option D).⁵ Therefore, identifying common patterns of multimorbidity may guide clinical decisions by helping clinicians to prioritize interventions that are most likely to have a positive impact on overall outcomes.

- 65-4. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 65*) Polypharmacy is typically defined as concomitant use of five or more medications (option A).⁶ The use of prescription medications and the prevalence of polypharmacy have increased markedly over the past decade.⁷ The number of chronic conditions and prescribing practices aligned with disease-based guidelines are directly correlated with polypharmacy.^{6,8} Approximately 40% of community-dwelling older adults take at least five medications (option B),⁶ and 20% take medications that may exacerbate coexisting conditions (option C).⁹ For example, arthritis is often treated with nonsteroidal anti-inflammatory drugs, which antagonize the effects of many cardiovascular medications (ACEIs, ARBs, diuretics) and also increase the risk for MI, HF, and worsening renal function (option D). The number of medications and treatment complexity are associated with nonadherence, drug-related adverse events, financial burden, and caregiver stress.^{6,10-16}
- 65-5. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 65*) Frailty is a geriatric syndrome that is characterized by a reduced physiologic reserve in multiple organ systems (eg, the brain or the endocrine, immune, musculoskeletal, or cardiovascular systems) to maintain homeostasis after a stressful event and an increased vulnerability to adverse health outcomes (option A).¹⁷ It is the most problematic manifestation of aging and contributes substantially to the heterogeneity in the health status of the aging population (option B). Several criteria for diagnosing frailty have been developed, yielding varying prevalence estimates in the general population, from < 5% using a specific physical performance-based definition to > 50% using a more comprehensive definition (option C).¹⁸ The *frailty phenotype*, derived from the Cardiovascular Health Study, is a widely accepted method for classifying older adults into robust, prefrail, or frail categories based on unintentional weight loss, weak handgrip strength, exhaustion, slow gait speed, and low physical activity.¹⁹ Persons with three or more of these criteria are considered frail (option D); those with one or two criteria are considered prefrail.
- 65-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 65*) Dementia affects 14% of adults age 70 years or older in the United States (option A), and the prevalence increases with age, from 5% in patients age 71 to 79 years to 37% in those over 90 years of age (option B).²⁰ Mild cognitive impairment, a less severe form of cognitive limitation with relative preservation of functional status, is present in 22% of people ≥ 70 years old (option C).²¹ The annual rate of progression from mild cognitive impairment to dementia is estimated to be about 12%.²¹ The prevalence of cognitive impairment in older adults with CVD is higher than that in the general population: 35% in patients undergoing coronary artery bypass graft (CABG) surgery²² and 47% in hospitalized patients with HF (option D).²³ The underlying mechanisms include hypoperfusion, oxidative stress, and inflammation, which lead to diverse cerebrovascular pathologies, including large cerebral infarcts, white matter lesions, lacunes, microinfarcts, and microbleeds (option E).²⁴
- 65-7. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 65*) Although the high prevalence of HF in elderly patients is partly related to improved survival from acute MI and other CVDs, other age-related factors contribute to the development of HF, including long-standing hypertension (option A) (present in 75% of patients with HF), vascular stiffness, left ventricular diastolic dysfunction, sinus node dysfunction, progressive valvular heart disease, coronary ischemia, and reduced responsiveness to β -adrenergic stimulation.²⁵ As a result, a gradual erosion in cardiovascular reserve with age results in an exponential rise in HF among older persons (option B). Studies in healthy older adults have confirmed that the effects of normal aging lead to altered preload, afterload, heart rate, and contractility—the four major determinants of cardiac output (option C)—thus resulting in a progressive decline in peak cardiopulmonary performance, even in the absence of clinically evident CVD.²⁶ Stated another way, an otherwise healthy 90-year-old person is likely to have exercise capacity and cardiovascular reserve equivalent to a younger person with New York Heart Association functional class III HF (option D).
- 65-8. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 65*) The role of intravenous antiplatelet therapy in ACS is difficult to define, both for younger and older patients. Glycoprotein IIb/IIIa inhibitors appear to reduce reinfarction and overall infarct size at the time of NSTEMI-ACS, with patients at higher risk deriving the most benefit (option A), but few studies have enrolled patients over age 75 (option B), and the risk of bleeding complications increases with age.^{25,27} One study of ACS patients demonstrated higher event rates in octogenarians randomized to glycoprotein IIb/IIIa inhibitor therapy,²⁸ and current guidelines recommend avoiding these medications entirely in the setting of fibrinolytic therapy for STEMI in patients ≥75 years of age (option C).²⁹ Because these drugs are associated with greater bleeding risks in the elderly, the use of glycoprotein IIb/IIIa inhibitors should probably be limited to select older individuals with high thrombosis risk and low bleeding risk (option D). The intravenous platelet inhibitor cangrelor has a different mechanism of action than the glycoprotein IIb/IIIa inhibitors, and clinical trials evaluating cangrelor demonstrated similar benefits among patients older and younger than age 75 years.³⁰ However, the magnitude of the bleeding risk associated with cangrelor remains unclear;³¹ thus, the safety of this drug in elderly patients requires further study.

- 65-9. The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 65*) The prevalence of symptomatic aortic stenosis (AS) increases from 0.2% in patients under age 60 to nearly 10% in those ≥ 80 years of age (option A).^{25,32} As a result, over 70% of all aortic valve procedures are performed in the geriatric population (option B), and AS is the most common valvular abnormality requiring surgical or percutaneous intervention (option C). Symptoms may not be as prominent in elderly patients with sedentary lifestyles (option D), resulting in delayed presentation or incidental diagnosis of severe AS at the time of presentation for other medical problems.²⁵ In addition, although physical findings are generally similar in younger and older patients, older patients with severe AS are less likely to exhibit delayed upstroke of the carotid pulse wave (pulsus tardus et parvus) as a result of increased arterial stiffness (option E).
- 65-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 65*) The progressive degeneration of sinus node pacemaker cells results in only 10% continuing to function normally by age 75 (option B).²⁵ Similar processes occur in the tissues surrounding the sinus node and within the conduction pathways, contributing to the development of sinoatrial exit block or atrioventricular nodal block.

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CHAPTER 66

Pericardial Diseases

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

- 66-1.** Which of the following is *correct* regarding the normal anatomy and physiology of the pericardium?
- A. It allows great distention of the cardiac chambers and increased cardiac filling
 - B. Congenital absence or surgical removal of the pericardium is fatal
 - C. The human pericardium consists of two distinct layers, the inner serosa and the outer fibrosa
 - D. Most of the innervation of the pericardium occurs via the vagus nerves
 - E. All of the above
- 66-2.** A 49-year-old man presents to clinic with pleuritic chest pain, myalgia, and fever. Which of the following findings is *not* a diagnostic criterion for acute pericarditis?
- A. New widespread ST elevation or PR depression on ECG
 - B. Sharp chest pain that is worse on inspiration
 - C. Fever > 38°C
 - D. Pericardial friction rub
 - E. New or worsening pericardial effusion
- 66-3.** A 63-year-old woman presents with recurrent pericardial disease. Which of the following is a Class I level A recommendation on the proper diagnosis and management of pericardial diseases?
- A. Corticosteroids should be prescribed as first choice in patients with acute pericarditis
 - B. Vasodilators and diuretics are recommended in the presence of cardiac tamponade
 - C. An absolute contraindication to draining a pericardial effusion includes a suspicion of bacterial etiology
 - D. Colchicine is a first-choice drug to be used as an adjunct to aspirin/NSAIDs to treat and prevent recurrent episodes of pericarditis
 - E. None of the above
- 66-4.** Which of the following is *not* a recommended therapeutic option for recurrent pericarditis?
- A. High-dose prednisone (1.0 to 1.5 mg/kg/d)
 - B. Triple therapy of aspirin, colchicine, and corticosteroids
 - C. Pericardiectomy
 - D. Low-dose prednisone for patients on oral anticoagulants
 - E. Aspirin/NSAID and colchicine
- 66-5.** A 40-year-old woman presents to the emergency room with chest pain, fever, and night sweats. She has recently returned from travelling in India and has lost 10 pounds. Which of the following findings is *not* consistent with a diagnosis of tuberculous pericarditis with pericardial effusion?
- A. Lack of signs and symptoms of pulmonary tuberculosis
 - B. Presence of pulsus paradoxus
 - C. Electrical alternans on ECG
 - D. Negative acid-fast bacilli staining and mycobacterium cultures on pericardial fluid
 - E. Elevated C-reactive protein
- 66-6.** Which of the following clinical presentations is consistent with cardiac tamponade?
- A. Pulmonary edema
 - B. Impaired ventricular diastolic filling

- C. Third heart sound
- D. Decreased central venous pressure
- E. All of the above

- 66-7.** A 63-year-old man is brought to the emergency room with altered level of consciousness and is found to be tachycardic and hypotensive. Echocardiography reveals a large pericardial effusion with echocardiographic evidence of tamponade. Which of the following is *not* appropriate in the subsequent management of this patient with cardiac tamponade?
- A. If a pericardial catheter is placed, removal of the intrapericardial catheter when the output is < 90 mL over a 24-hour period
 - B. Prompt needle pericardiocentesis to aspirate all the pericardial fluid
 - C. Pericardiocentesis should be guided by echocardiography to prevent tissue injury
 - D. If a pericardial catheter is placed, reassessment of effusion size and areas of loculation before catheter removal
 - E. All of the above are correct
- 66-8.** Which of the following statements about constrictive pericarditis is *correct*?
- A. It is twice as prevalent in women as in men (2:1 ratio)
 - B. The thickened pericardium has decreased compliance, resulting in ventricular interdependence
 - C. Orthopnea and paroxysmal nocturnal dyspnea are typically observed
 - D. Patients often present with features of left-heart failure
 - E. None of the above
- 66-9.** Which of the following is most likely to provide definitive treatment for symptomatic patients with constrictive pericarditis?
- A. Anti-inflammatory therapy
 - B. Pericardiocentesis
 - C. Pericardiectomy
 - D. Close follow-up
 - E. None of the above
- 66-10.** A 55-year-old woman presents to your clinic with vague chest pain and dyspnea. A chest radiograph reveals a mass in the right costophrenic angle. CT of the chest suggests a pericardial cyst. Which of the following is *correct*?
- A. Pericardial cysts are smooth, thin-walled structures usually filled with pus
 - B. The recommended therapeutic course is observation of the patient
 - C. Pericardial cysts are usually symptomatic and tend to increase in size over time
 - D. The patient's symptoms are likely unrelated to the cyst
 - E. Percutaneous drainage of the cyst is recommended for asymptomatic patients

ANSWERS

- 66-1. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 66*) The human pericardium has two distinct layers; the serosa is composed of a single column of mesothelial cells that surrounds all four cardiac chambers and the proximal great vessels and reflects on itself to form the inner surface of the fibrosa, a fibrocollagenous structure (option C). This monolayer of serosal cells covering the surface of the heart and epicardial fat is also called the visceral pericardium, whereas the fibrosa and the reflection of the serosa make the parietal pericardium.
- Most of the innervation of the pericardium occurs via the phrenic nerves (C4–C6), which course anteriorly (option D); this is particularly relevant during pericardiectomy. No adverse consequences follow congenital absence or surgical removal of the pericardium (option B). However, the pericardium serves many important (although subtle) functions. It limits distension of the cardiac chambers and facilitates the interaction and coupling of the ventricles and atria (option A). Limitation of cardiac filling volumes by the pericardium may also limit cardiac output and oxygen delivery during exercise.
- 66-2. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 66*) The clinical diagnosis of acute pericarditis is established when two of four clinical criteria are satisfied ([Table 66-1](#)). Acute pericarditis is usually characterized by sharp retrosternal pain (option B) that is aggravated by lying down and relieved by sitting up; its onset is often heralded by a prodrome of fever, malaise, and myalgia. The most specific physical sign can be the presence of a pericardial friction rub (option D), which is identifiable in no more than a third of cases. Within a few hours of the onset of chest pain, typical ECG changes include ST-segment elevations and depression of the PR segment (except in lead aVR), which can persist for hours or days (option A). This is the first ECG stage of pericarditis, followed by normalization of the ST segments (stage 2), T-wave inversions (stage 3), and finally, normalization again (stage 4). This is different from myocardial

infarction, wherein T-wave inversions often begin while the ST segments are still elevated. In addition, echocardiographic identification of pericardial effusion confirms the clinical diagnosis of acute pericarditis (option E). Elevated fever (option C) is a major indicator of poor prognosis but is not a diagnostic criterion.

TABLE 66-1 Definition and Diagnostic Criteria for Acute Pericarditis

Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria:
(1) pericarditic chest pain
(2) pericardial rubs
(3) new widespread ST elevation or PR depression on ECG
(4) pericardial effusion (new or worsening)
Additional supporting findings:
Elevation of markers of inflammation (ie, C-reactive protein, erythrocyte sedimentation rate, and white blood cell count);
Evidence of pericardial inflammation by an imaging technique (computed tomography, cardiac magnetic resonance).

66-3. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 66*) Treatment of pericardial disease is challenging because there is a paucity of randomized, placebo-controlled trials that identify appropriate therapy and help with clinical decision making. Table 66-2 summarizes the main recommendations of the 2015 ESC guidelines.¹ Colchicine is a first-line therapy to be used as adjunct to aspirin/NSAIDs or corticosteroids to treat and prevent pericarditis, either in acute or recurrent cases (Class I recommendation, level of evidence: A) (option D). Corticosteroids should not be prescribed as first choice in patients with acute pericarditis, given the risk of recurrence (Class III recommendation, level of evidence: C) (option A). The essential indications to drain a pericardial effusion include: cardiac tamponade (therapeutic pericardiocentesis), a suspicion of bacterial or neoplastic etiology, and persistent moderate to large pericardial effusion without response to medical therapy (Class I recommendation, level of evidence: C) (option C). Vasodilators and diuretics are not recommended in the presence of cardiac tamponade (Class III recommendation, level of evidence: C) (option B).

TABLE 66-2 Summary of the 2015 European Society of Cardiology Guidelines on the Diagnosis and Management of Pericardial Diseases

	Indication	Evidence
Acute and recurrent pericarditis		
A triage is recommended to identify high-risk patients who should be admitted to hospital. Low-risk patients can be managed as outpatients.	Class I	Level B
Colchicine is now a first-choice drug to be used as adjunct to aspirin/NSAID or corticosteroids to treat and prevent pericarditis either in acute or recurrent pericarditis (weight-adjusted doses are recommended without a loading dose; eg, 0.5 mg twice a day for 3 months in acute pericarditis and 6 months in recurrent pericarditis; colchicine should be given only as 0.5 mg once for patients > 70 kg).	Class I	Level A
Levels of C-reactive protein are useful to guide the treatment duration and assess the response to treatment in acute and recurrent pericarditis; anti-inflammatory therapy should be maintained until symptom resolution and C-reactive protein normalization.	Class IIa	Level C
Corticosteroids should not be prescribed as first choice in patients with acute pericarditis since it may favor chronicization.	Class III	Level C
Pericardial effusion		
The essential indications to drain a pericardial effusion include: (1) cardiac tamponade (therapeutic pericardiocentesis), (2) a suspicion of bacterial or neoplastic aetiology, and (3) persistent moderate to large pericardial effusion without response to medical therapy.	Class I	Level C
A triage system is proposed also for the management of pericardial effusion and is essentially based on the following: (1) recognize cardiac tamponade and possible bacterial or neoplastic etiologies, (2) exclude concomitant pericarditis or treat as pericarditis, (3) identify associated underlying diseases, and (4) if chronic and large (> 20 mm), consider pericardial drainage to prevent cardiac tamponade during follow-up.	Class I	Level C
Treatment of pericardial effusions should be tailored as much as possible to the underlying etiology.	Class I	Level C
Cardiac tamponade		
In a patient with clinical suspicion of cardiac tamponade, echocardiography is recommended as the first imaging technique to evaluate the size, location, and degree of hemodynamic impact of the pericardial effusion.	Class I	Level C

Urgent pericardiocentesis or cardiac surgery is recommended to treat cardiac tamponade.	Class I	Level C
A judicious clinical evaluation including echocardiographic findings is recommended to guide the timing of pericardiocentesis.	Class I	Level C
Vasodilators and diuretics are not recommended in the presence of cardiac tamponade.	Class III	Level C
Constrictive pericarditis		
CT and CMR are indicated for the evaluation of a suspected constrictive pericarditis as second-level imaging techniques after echocardiography.	Class I	Level C
Cardiac catheterization is indicated only in complex cases when noninvasive imaging does not provide a clear-cut diagnosis or provides conflicting results.	Class I	Level C
The mainstay of therapy for chronic constriction is radical pericardiectomy, but it is acknowledged that there is a need to assess the possible presence of pericardial inflammation (eg, elevation of C-reactive protein, pericardial inflammation on CT/CMR) as precipitating cause in new-onset cases in order to treat with empiric anti-inflammatory therapy.	Class I	Level C
Diagnostic workup of pericardial diseases		
First diagnostic evaluation in a patient with a clinical suspicion of pericardial disease should include: focused history and physical examination, ECG, chest x-ray, and routine blood tests, including markers of myocardial inflammation and lesion and renal function.	Class I	Level C
Echocardiography is the first essential diagnostic imaging tool, whereas CT and CMR are second-level imaging techniques for specific indications.	Class I	Level C
Additional diagnostic testing should be targeted and clinically guided.	Class I	Level C
Main specific forms		
<i>Tuberculosis</i>		
Empiric antituberculous therapy is only recommended in countries where tuberculosis is endemic and the disease is highly probable in the setting of a patient with pericarditis and pericardial effusion.	Class I	Level C
In cases with an established diagnosis of tuberculous pericarditis, standard antituberculous therapy is recommended for 6 months and prevents the evolution to constrictive pericarditis.	Class I	Level C
In patients with tuberculous pericarditis with features of constriction and not responding to antituberculous therapy, pericardiectomy is recommended after 4–8 weeks of medical therapy.	Class I	Level C
<i>Neoplastic pericardial diseases</i>		
The definite diagnosis of neoplastic pericardial disease relies on the evidence of neoplastic cells on cytology of pericardial fluid.	Class I	Level B
Pericardial biopsy should be considered for the final etiologic diagnosis in selected cases.	Class IIa	Level B
Tumor markers in pericardial fluid may be helpful to differentiate a benign vs a malignant pericardial effusion.	Class IIa	Level B
In cases with a confirmed diagnosis of neoplastic pericardial disease, systemic antineoplastic treatment is indicated.	Class I	Level B
Extended pericardial drainage is recommended to prevent recurrent cardiac tamponade and pericardial effusion and to provide a way for intrapericardial therapy.	Class I	Level B
Intrapericardial therapy with cytostatic agents should be considered to treat neoplastic pericardial disease.	Class IIa	Level B

Abbreviations: CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiography; NSAID, nonsteroidal anti-inflammatory drugs.

66-4. The answer is A. (*Hurst's The Heart, 14th Edition, Chap. 66*) Recurrent pericarditis is one of the most troublesome complications of pericarditis, occurring in one-third of cases. The mainstay of therapy for recurrences is similar to that for acute pericarditis: aspirin or an NSAID plus colchicine at the same doses that are recommended for acute pericarditis (option E). Corticosteroids should be considered as a second-line therapy for patients with contraindications for or failure of aspirin/NSAIDs or patients with specific indications (eg, pregnant patients, patients with a systemic inflammatory disease already on corticosteroids, patients with renal failure, patients on oral anticoagulant therapies to avoid interference with aspirin/NSAIDs) (option D). If used, low to moderate doses (eg, prednisone 0.2 to 0.5 mg/kg/d or equivalent) are indicated because high doses (eg, prednisone 1.0 to 1.5 mg/kg/d) are associated with a high rate of severe side effects (up to 25%) with more drug withdrawals, drug-related hospitalization, and recurrences (option A). In more difficult cases, aspirin or NSAID, colchicine, and corticosteroids may be used together as a triple therapy to achieve better control of symptoms (option B).² After failure of medical therapy, pericardiectomy can be considered (option C), although it should be performed in centers with specific expertise in such surgery to achieve the best outcomes.³

66-5. The answer is D. (*Hurst's The Heart, 14th Edition, Chap. 66*) Tuberculosis is a major cause of pericarditis in nonindustrialized countries but an uncommon cause in developed countries with a low prevalence of tuberculosis. Tuberculous pericarditis results from hematogenous spread of primary tuberculosis or from the breakdown of infected mediastinal lymph nodes, with the result that affected individuals generally lack the typical symptoms and signs of pulmonary tuberculosis (option A). Early signs include fever, weight loss, and night sweats. Essentially, all causes of pericarditis can manifest as pericardial effusion. In developing countries, tuberculosis continues to be the predominant etiology, accounting for 50% to 60% of cases.⁴ Findings suggestive of pericardial effusion with tamponade physiology (that are nonspecific to tuberculous pericardial disease, however) include an elevated pulsus paradoxus (option B) and ECG findings of low QRS voltage and electrical alternans (option C). Bacterial and mycobacterial cultures should be

performed if bacterial infection or tuberculosis is suspected, respectively. However, TB is a slow-growing organism, and cultures can take weeks to become positive. Acid-fast bacilli staining (option D), adenosine deaminase, pericardial lysozyme, and interferon- γ levels, as well polymerase chain reaction testing, should be added in the evaluation of tuberculous pericarditis. Nonspecific blood markers of inflammation, such as the erythrocyte sedimentation rate, C-reactive protein (option E), and white blood cell count, usually increase in cases of pericarditis and can support the diagnosis.

- 66-6. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 66*) Cardiac tamponade corresponds to a corollary of hemodynamic derangements that are secondary to increased intrapericardial pressure. As intrapericardial pressure rises in patients with cardiac tamponade, elevated pericardial pressure is transmitted to all four chambers, affecting diastolic filling. Inspection of the jugular veins will show elevation in central venous pressure (option D); venous distention may or may not be present. Analysis of the venous wave contour will reveal absence or blunting of the y descent, representing impaired ventricular diastolic filling (option B).
- Cardiac auscultation might reveal distant heart sounds. Because early diastolic filling is profoundly impaired, a third heart sound should not be present (option C); its occurrence suggests an alternative diagnosis. For unclear reasons, tamponade does not usually lead to pulmonary edema (option A); the lungs are often clear on auscultation in patients with isolated cardiac tamponade. Rather, hemodynamic compromise is the more striking finding.
- 66-7. The answer is A.** (*Hurst's The Heart, 14th Edition, Chap. 66*) Cardiac tamponade is a cardiac emergency and should be treated with prompt needle pericardiocentesis (option B) unless it is caused by aortic dissection. The goal should be aspiration of all pericardial fluid. The procedure should be done with transthoracic echocardiographic guidance by an experienced operator (option C). During echo-guided pericardiocentesis, the largest collection of fluid in closest proximity to the chest wall should be identified, defining the optimal site for needle entry. Echocardiography also confirms the absence of interposed lung or liver tissue. Complications include cardiac or coronary perforation, hemothorax or liver injury, pneumothorax, and pneumopericardium. The daily output of pericardial fluid is recorded. The pigtail catheter should not be removed until the output is < 30 mL over a 24-hour period (option A). Before the intrapericardial catheter is removed, a limited echocardiogram is often repeated to reassess the effusion size and areas of loculation (option D).
- 66-8. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 66*) Constrictive pericarditis results from inflammation and/or scarring of the pericardium, leading to impairment of cardiac filling. The disease also appears to favor men over women (2:1 ratio) (option A). Given the abnormal pericardial compliance, diastolic filling is significantly impaired in patients with constrictive pericarditis (steeper increase in pressure per change in volume in the pressure–volume curve). As a consequence, cardiac filling pressures increase, and cardiac output falls as stroke volume decreases. The thickened pericardium has limited expansion, and cardiac chambers “compete” for pericardial space during diastolic filling. With respiration, an increase in preload in one ventricle occurs at the expense of filling in the other (ventricular interdependence) (option B). Patients with constrictive pericarditis typically present with features of right-sided heart failure (option D), manifested by elevated venous pressure, ascites, and leg edema. Orthopnea and paroxysmal nocturnal dyspnea are not usually observed and suggest another etiology (option C).
- 66-9. The answer is C.** (*Hurst's The Heart, 14th Edition, Chap. 66*) Although patients presenting with constrictive pericarditis and evidence of active pericardial inflammation (either by CMR or elevated inflammatory markers) might respond to anti-inflammatory therapy (Class IIb recommendation; level of evidence: C) (option A), therapeutic pericardiectomy is the recommended treatment for symptomatic patients with constrictive pericarditis (Class I recommendation; level of evidence: C) (option C). Pericardiectomy is the surgical removal of the pericardium, and the procedure is applicable to all variants of pericardial disease. Some patients presenting with cardiac tamponade demonstrate features of constrictive pericarditis immediately after pericardiocentesis is performed and tamponade relieved, such as in the case of those with effusive constrictive pericarditis. In such cases, therapy should be focused on treating active inflammation; a subset of patients might develop chronic constrictive pericarditis and require pericardiectomy following the pericardiocentesis (option B). Therefore, close follow-up of patients with effusive-constrictive pericarditis is recommended (option D).
- 66-10. The answer is B.** (*Hurst's The Heart, 14th Edition, Chap. 66*) Pericardial cysts are smooth, thin-walled structures filled with clear fluid (hence the term spring water cysts) (option A). Patients with pericardial cysts are usually asymptomatic, and the cysts tend not to increase in size (option C). Some patients with pericardial cysts complain of atypical chest pain or dyspnea, most likely as a result of compression of contiguous structures (option D). For patients with symptoms related to the pericardial cyst, percutaneous drainage or surgical removal can be performed (option E).⁵ However, given the risks associated with both procedures and the benign, well-tolerated course of the disease, observation is likely most appropriate for the majority of patients with pericardial cysts (option B).

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